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Total synthesis of nahuoic acid A *via* a putative biogenetic intramolecular Diels–Alder (IMDA) reaction†

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Inspired by the biogenetic proposal of an intramolecular Diels–Alder (IMDA) cycloaddition, the total synthesis of natural product nahuoic acid A, a cofactor-competitive inhibitor of the epigenetic enzyme lysine methyl transferase SETD8, has been carried out. A non-conjugated pentaenal precursor was synthesized with high levels of stereoselectivity at seven stereogenic centers and with the appropriate control of double bond geometries. Although the IMDA reaction of the non-conjugated pentaenal using Me_2AlCl for catalysis at −40 °C selectively afforded the *trans*-fused diastereomer corresponding to the *Re-endo* mode of cycloaddition, under thermal reaction conditions it gave rise to a mixture of diastereomers, that preferentially formed through the *exo* mode, including the *cis*-fused angularly-methylated octahydronaphthalene diastereomer precursor of nahuoic acid A. The natural product could be obtained upon oxidation and overall deprotection of the hydroxyl groups present in the *Si-exo* IMDA diastereomer.

A Introduction

Nahuoic acid A (**1a**) was first isolated in 2013 from cultures of *Streptomyces* sp. (isolate RJA2928) in a marine sediment collected near the passage Padana Nahua in Papua New Guinea[1a] using a chemical genetics approach.[1b] The structure of **1a** was shown to contain an octahydronaphthalene core with seven contiguous stereocentres and unsaturated substituents of *E* geometry at C4 and C13, namely a 2-methylpropenoic acid, and a 2,4,10-trimethylundec-9-ene-3,5,7-triol side chain with four additional stereogenic centers, respectively. The relative configuration of the stereogenic elements of this polyketide natural product was determined[1a] through comprehensive analysis of ^{1}H-NMR spectroscopic data using a combination of trNOESY and gCOSY60 correlations, and the absolute configuration was assigned by NMR analysis of the acetonides[2] and modified Mosher ester derivatives.[3]

Additional family members, termed nahuoic acids B-E (**1b–d**; **2a–c**; Fig. 1), were further isolated from the same genus.[4] Structural differences among the series relative to parent nahuoic acid A (**1a**) rely on the level and positional oxidation of the octahydronaphthalene core (**1b–c**) and on the length and number of hydroxyl-containing stereocenters on the polyhydroxylated side chain at C13 (**2a–c**). A unified nomenclature of the natural nahuoic acid family members was later proposed by A. B. Smith III *et al.*, as depicted in Fig. 1.[5]

A significant decrease in cell proliferation of the osteosarcoma U2OS cells ($IC_{50} = 65 \pm 2$ μM), and the SUM159 ($IC_{50} = 45$ μM), and MDA-MB-436 ($IC_{50} = 85$ μM) breast cancer cells was noticed after treatment with nahuoic acid A (**1a**).[1a,4b] In contrast to parent **1a**, structurally similar analogs B-E (**1b–d** and **2a–c**) were found to be inactive in the same assay.[4a] However, the polyacetylated derivative of **1a** (not shown) was reported to

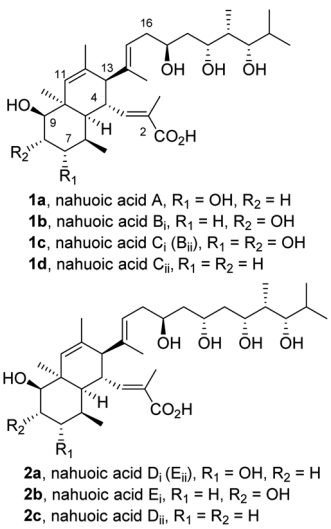

Fig. 1 Structure and unified nomenclature of nahuoic acids.[5]

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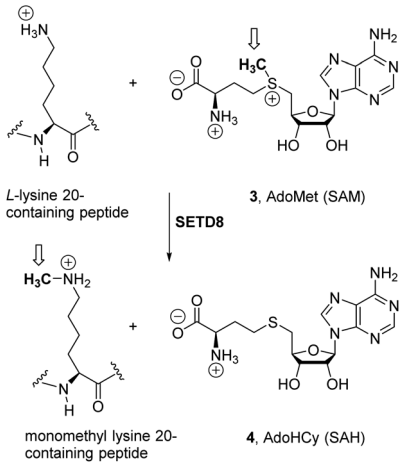


Scheme 1 Histone lysine methylation catalyzed by lysine methyl transferases (KMTs).

inhibit the proliferation of certain cancer cell lines with moderate potency.[4b]

The inhibition of proliferation of several cancer cell lines by **1a**[1a] was causally linked to the competitive inhibition (K_i = 2 μM) with the binding of biological cofactor *S*-adenosylmethionine (SAM or AdoMet **3**, Scheme 1) to the epigenetic enzyme SETD8.[4b,6] SETD8, also known as SET8/PR-Set7/KMT5A, is a member of the histone methyltransferase (HMT) family,[7] which is implicated, along with other enzymes, in the chemical modifications of histones, a group of highly basic proteins that pack the DNA into the nucleosomes in eukaryotic cells.

In particular, the methylation status of specific lysine residues in histone proteins is tightly regulated by the competitive actions of the lysine methyl transferase (KMT) and lysine demethylase (KDM) families of epigenetic enzymes.[7c–f,8a,b] Since the methylation status of histones plays important roles in the regulation of transcription and the maintenance of genomic integrity in eukaryotes, the lack of control of this epigenetic modification from its normal status appears to be related to inflammation and to several diseases, including leukaemia and breast and prostate cancer.[9a,b]

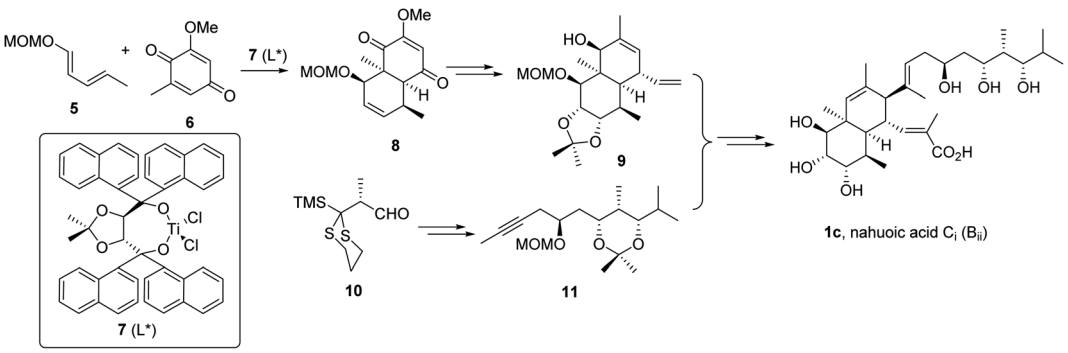
Mechanistically, *ca.* 100 KMT family members[7b] promote an S_N2-type reaction (Scheme 1) through an early transition state[10] for the transfer of the methyl group of cofactor SAM (**3**) to a partially deprotonated terminal ε-amine lysine group, releasing *S*-adenosylhomocysteine (SAH, AdoHCy, **4**, Scheme 1).[11] SETD8 (ref. 12) has been shown to monomethylate the ε-amino group of lysine 20 on histone 4 (H4K20me)[13] and also specific lysines of proliferating cell nuclear antigen (PCNA)[14] and p53/TP53.[15] This KMT enzyme has been found to be overexpressed in several types of cancer,[12a,15] and appears to play an important role in the progression from the *S* phase of the cell cycle.[16]

Since nahuoic acid A (**1a**) is the first reported cofactor-competitive inhibitor of SETD8, and its promising biological activities are putatively linked to SETD8 inhibition,[6,7d–f,17] its structure can be considered as a challenging lead for further development. In fact, our interest in the synthesis and biological evaluation of epigenetic modulators[18a–d] inspired by the structure of natural products made nahuoic acid A (**1a**) an attractive target candidate for synthesis.

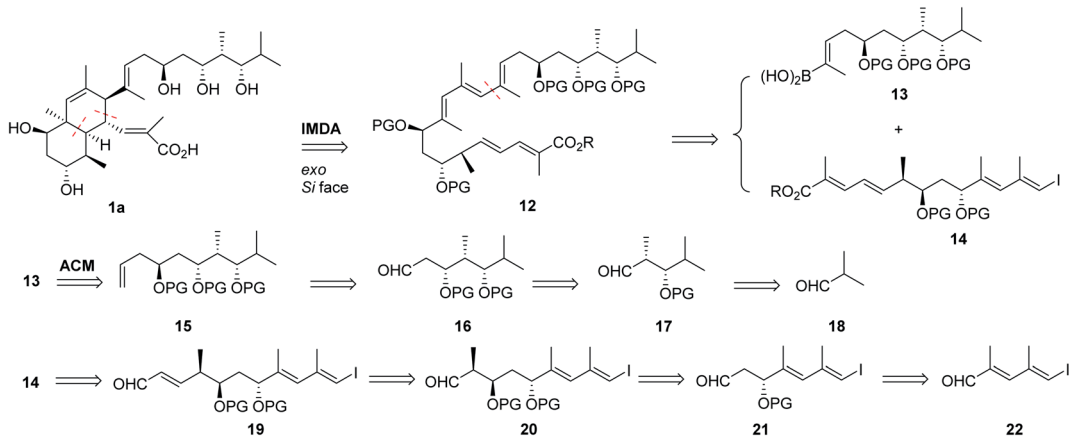
While our efforts to synthesize nahuoic acid A (**1a**) were in progress,[19] the total synthesis of nahuoic acid Ci (**1c**, Scheme 2) was reported.[5]

The *cis*-octahydronaphthalene fragment **9** was obtained by the intermolecular Diels–Alder cycloaddition reaction of components **5** and **6** promoted by enantiopure TADDOL-derived titanium complex **7** to afford intermediate **8**, followed by functional group interconversion and generation of additional stereocenters. The trihydroxylated side chain functionalized as internal alkyne **11** was constructed from intermediate **10** by the anion relay chemistry (ARC) approach[20] (Scheme 2), and connected to **9** by application of the Micalizio protocol.[21]

Our retrosynthetic analysis of the nahuoic acid skeleton (Scheme 3) was instead inspired by the hypothetical biogenesis of the octahydronaphthalene core structure of **1a** through an intramolecular Diels–Alder (IMDA) reaction[22] of an appropriate pentaenoate precursor **12**. In order to afford the desired diastereomer, the pentaenoate of *E* geometry of **12** should undergo intramolecular cycloaddition following an *exo* orientation towards the diene of the reacting *Si* face of the dienophile. The central conjugated triene fragment of **12** would instead be obtained by a Suzuki–Miyaura cross-coupling[23] of two components of similar complexity, namely internal boronic acid **13** and terminal non-conjugated iodotetraenoate **14**. Several



Scheme 2 Smith's total synthesis of nahuoic acid Ci (Bii, **1c**).[5]

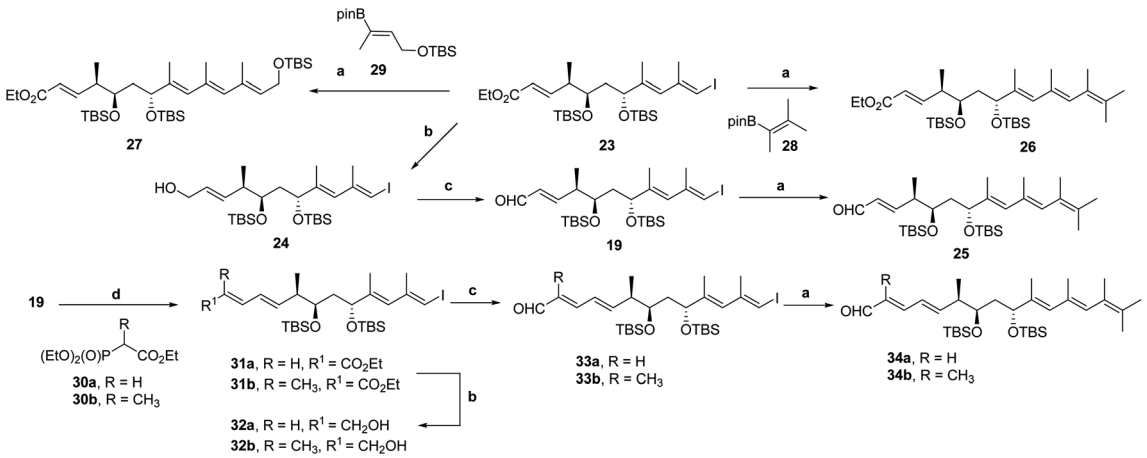


Scheme 3 Biogenetically-inspired retrosynthetic analysis of nahuoic acid A (**1a**).

approaches could be envisaged for the construction of these polypropionate-like polyols, and one of them is illustrated in Scheme 3. The alkenylboronic acid **13** was proposed to be generated by acyclic cross-metathesis of an alkenyl boronate and homoallylic alcohol **15** containing a formal protected 1,3,5-triol fragment. The latter would be prepared by diastereoselective allylation of aldehyde **16** containing three contiguous stereocenters, which could arise from protected aldol **17**, the product expected from a diastereo- and enantioselective aldol reaction of isobutyraldehyde **18** and propanal surrogates. Iodotetraenoate **14** would instead be obtained by unsaturated chain extension of precursor iodotrienal **19** and the latter from protected aldol **20**, which could be generated following similar protocols already described for **16**. The synthesis of the aldol precursor **21** could be based on the enantioselective allylation of δ-iododienal **22** followed by ozonolysis. The combination of ligand-dependent enantioselective reactions and substrate-promoted diastereoselective bond-forming reactions should allow us to set up the relative and absolute configurations of the intermediates on route to the natural product.

An additional interest of the synthetic proposal was the exploration of the intramolecular Diels–Alder reaction (IMDA)[22] of **12** for the construction of the octahydronaphthalene core of nahuoic acid A (**1a**). This biogenetic route appears to be feasible in nature and a series of putative Diels–Alderase enzymes have been structurally and functionally characterized,[24] and grouped under the general family of "biosynthetic pericyclases".[25a,b] Members of natural [4 + 2]-cyclases[25c,d] including enzymes involved in inverse electron-demand Diels–Alder reactions[25e] have been identified in nature, in some cases as part of enzymatic cascade reactions that generate further biosynthetic complexity.[25f–i]

We have already reported[19] the synthesis of functionalized tetraenal **25** and tetraenoates **26–27** (Scheme 4), which are shorter unsaturated analogues of pentaenoate **12** (Scheme 3), as model systems to test the feasibility of the IMDA tactic[22] to



Scheme 4 Synthesis of non-conjugated tetraenals, tetraenoates and pentaenals for the preparation of the octahydronaphthalene core of nahuoic acid model systems. Reagents and reaction conditions: (a) **28** or **29**, $Pd(PPh_3)_4$ (cat), 10% aq. TlOH, THF, 25 °C, 3 h (97% for **26**; 99% for **27**; 83% for **25**; 92% for **34a**; 99% for **34b**). (b) DIBAL-H, THF, −78 °C, 6 h (99% for **24**, **32a** and **32b**). (c) MnO_2, Na_2CO_3, CH_2Cl_2, 25 °C, 16–24 h (92% for **19**; 92% for **33a**; 95% for **33b**). (d) $(EtO)_2P(O)CH_2CO_2Et$ **30a** or $(EtO)_2P(O)CH(CH_3)CO_2Et$ **30b**, *n*-BuLi, DMPU, THF, −78 to 25 °C, 16 h (77% for **31a**, 1 : 0.2 *E*/*Z* ratio; 89% for **31b**, 1 : 0.1 *E*/*Z* ratio).

achieve **1a**. The IMDA reaction of tetraenal **25** led, under both purely thermal and Lewis acid-promoted IMDA reaction conditions, to the octahydronaphthalenes as mixtures of two *cis*-octahydronaphthalenes and a *trans*-diastereoisomer, thus confirming the formation of products through both *exo* approaches and through one of the putative *endo* alternatives, the latter being of lower energy.[19]

We wish to report herein the full account of our synthesis of nahuoic acid A (**1a**) based on the putative biogenetic proposal using the corresponding pentaenals related to **12** (Scheme 3), which required the construction of the entire unsaturated acyclic skeleton in a highly diastereo- and enantioselective fashion.

B Results and discussion

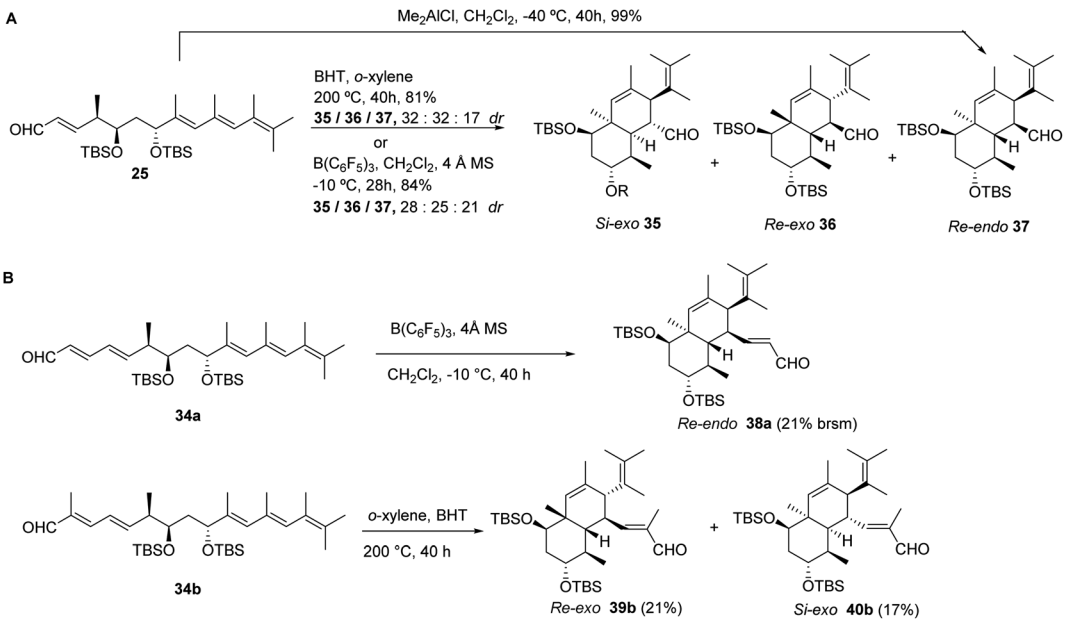
Non-conjugated tetraenal and pentaenal model systems and IMDA reaction

For the preparation of functionalized tetraenes **25**, **26** and **27** (Scheme 4) containing the acyclic skeletons required for the IMDA reaction,[19] a Suzuki–Miyaura cross-coupling[23] was chosen as the last step of the synthesis. Under the conditions developed by Kishi for alkene–alkene cross-coupling (catalysis by $Pd(PPh_3)_4$ in THF and 10% aqueous TlOH)[26] tetraenes **25**, **26** and **27** were synthesized[19] starting from iodotrienoate **23** or iodotrienal **19** and either commercial alkenylpinacol boronate **28** or analogue **29**, itself obtained by regio- and stereoselective borylation of protected but-2-yn-1-ol.[27]

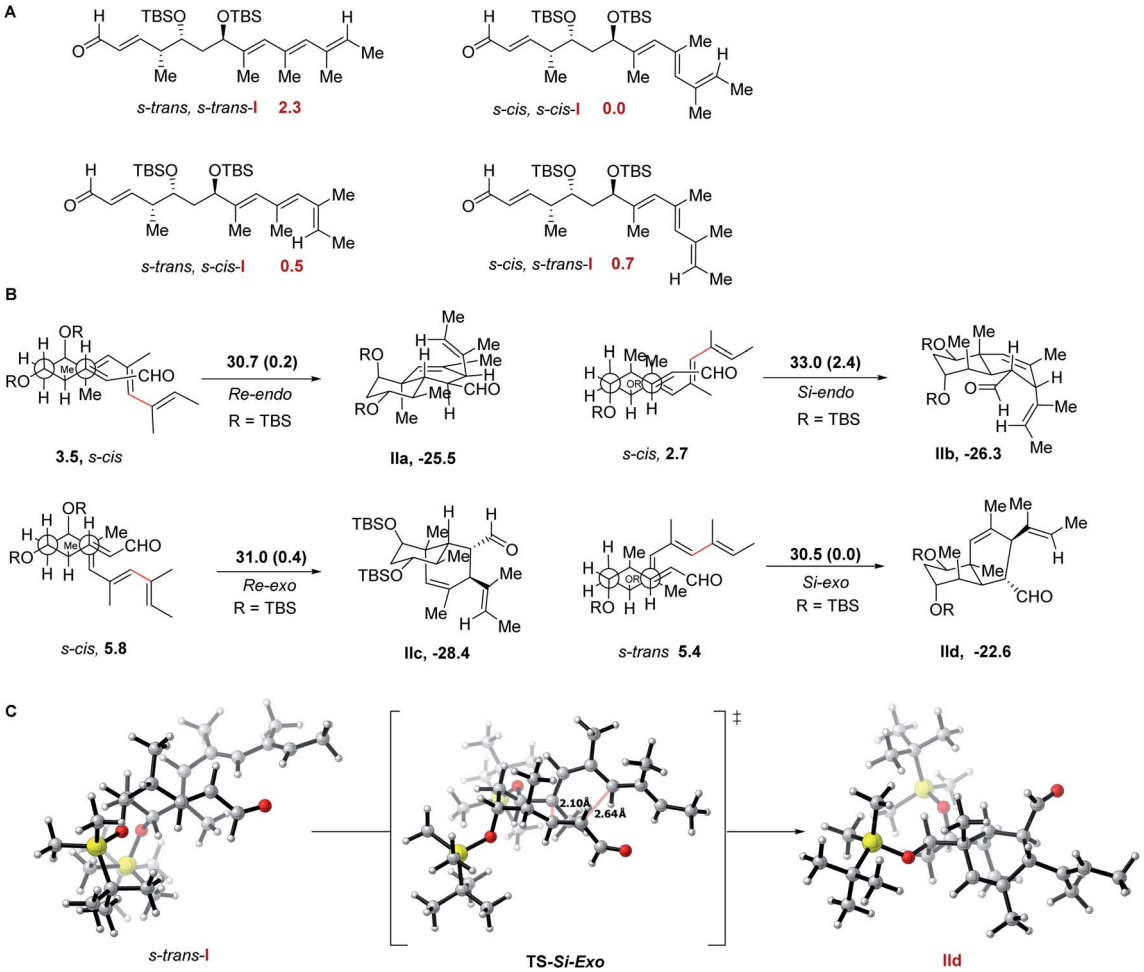
In addition, model pentaenals **34a** and **34b** were constructed by unsaturated chain extension of iodotrienal **19**.[19] The Horner–Wadsworth–Emmons (HWE) reaction[28] of **19** (ref. 19) with the corresponding anions of phosphonates **30a** and **30b**, generated with *n*-BuLi and DMPU in THF, afforded conjugated dienoates **31a** and **31b**, respectively (Scheme 4), whereas the reaction with phosphonate **30a** afforded a 5 : 1 *E*/*Z* mixture of isomers of **31a** in 77% yield, and using the methyl-substituted analogue **30b** both the isomer ratio (10 : 1) of pentaenoate **31b** and the yield of the HWE reaction (89%) were higher. Reduction of **31a** and **31b**27 with DIBAL-H afforded allylic alcohols **32a** and **32b**, respectively, in quantitative yield, from which conjugated dienals **33a** and **33b**, respectively, were obtained uneventfully (92 and 95% yield, respectively) upon allylic oxidation with MnO_2 and Na_2CO_3. The Suzuki–Miyaura cross-coupling reaction[23] of **33a** or **33b** with **28** under the conditions indicated above gave rise to non-conjugated pentaenals **34a** and **34b** in 92 and 99% yield, respectively (Scheme 4).

No conversion was noticed when solutions of ethyl tetraenoates **26** or **27** in toluene-d_8 where heated up to 120 °C in the presence of BHT.[29] Further temperature increase up to 165 °C led to extensive decomposition. Strikingly, although tetraenal **25** proved to be unreactive when treated with Me_2AlCl in CH_2Cl_2 at −78 °C for 24 h,[30] a smooth and quantitative conversion to a cyclic derivative was observed upon increasing the temperature to −40 °C and stirring for 40 h. Exhaustive NMR studies suggested structure **37** (Scheme 5) for the octahydronaphthalene diastereoisomer obtained in the IMDA reaction, which was further confirmed by X-ray diffraction analysis.[19] This compound must likely originate from the *Re-endo* orientation of the dienophile fragment relative to the reacting diene in non-conjugated tetraenal **25**.

Heating instead a solution of tetraenal **25** in *o*-xylene at 200 °C for 40 h afforded a mixture of three major compounds, which were identified after chromatographic separation as the octahydronaphthalenes *Si-exo* **35**, *Re-exo* **36**, and *Re-endo* **37** diastereomers, in a 40 : 40 : 20 isomer ratio, respectively, and 81% overall yield (Scheme 5). The structure of **35** was obtained by X-ray single crystal diffraction analysis,[19] which allowed us to



Scheme 5 IMDA reactions of non-conjugated tetraenal **25** (A) and pentaenals **34a and b** (B) under different reaction conditions.



Scheme 6 (A) Lowest energy conformations of non-conjugated tetraenal model system I. (B) Lowest energy approaches computed for the thermal IMDA reaction to afford the *cis*-octahydronaphthalene II. (C) Representation of the Si-*exo* approach. All computations were carried out at the ωB97XD/DefTZVP (SMD, toluene) level of theory. Relative energies are given in kcal mol^{-1}.

confirm the absolute configuration of the octahydronaphthalene core present in natural product **1a**. Although ^{1}H-NMR analysis revealed the presence of minor components (<10% yield) in the reaction mixture, signals putatively assigned to the *Si-endo* diastereomer were not clearly identified. The use of stronger and bulkier Lewis acid $B(C_6F_5)_3$ in DA reactions of acyclic dienes with unsaturated aldehydes has been found to alter the innate diastereoselectivity of these processes, leading predominantly to the formation of the *exo* adducts.[31]

The effect has been proposed to be merely steric in origin, as the bulky $B(C_6F_5)_3$ complexed to the aldehyde carbonyl group would disfavor the *endo* transition state.[32] In our case, it was found that upon stirring a solution of tetraenal **25** in CH_2Cl_2 with $B(C_6F_5)_3$ (0.5 mol equiv.) at −10 °C for 48 h, a mixture of the *Si-exo* **35**, *Re-exo* **36** and *Re-endo* **37** octahydronaphthalenes, in a 38 : 34 : 28 isomer ratio, respectively, was isolated in 74% overall yield (Scheme 5).

Unfortunately, all attempts to perform the unsaturated chain extension of aldehyde *Si-exo* **35** either using the HWE reaction[28] with phosphonate **30b** (Scheme 4, by heating up to 40 °C), the Wittig reaction[28a,33,34] with the phosphonium salt analogue or the less-sterically demanding Peterson olefination[35] with the trialkylsilyl derivative as the reagent, proved to be fruitless, and the alkenyloctahydronaphthalene carboxaldehyde *Si-exo* **35** was recovered.

Vinylogous pentaenals **34a** and **34b** were alternatively treated under thermal or Lewis-acid catalyzed reaction conditions (Scheme 5). Upon activation with $B(C_6F_5)_3$ in CH_2Cl_2 containing 4 Å MS at −10 °C (ref. 31) pentaenal **34a** afforded an octahydronaphthalene skeleton, which was identified through NOESY-1d experiments as the *Re-endo* cycloadduct **38a** (21% yield) and unreacted substrate **34a** (32% yield), accompanied by an additional compound (15% yield), which could not be fully characterized. The methyl-substituted pentaenal analogue **34b** proved to be unreactive under the same reaction conditions, suggesting a limitation of the $B(C_6F_5)_3$-based activation procedure for more sterically hindered aldehydes. As an alternative, heating **34b** to 200 °C in *o*-xylene containing BHT as the radical inhibitor afforded a mixture of products, which were further characterized by NMR spectroscopy following HPLC purification (Scheme 5). Octahydronaphthalenes resulting from *Re-exo* **39b** (31%) and *Si-exo* **40b** (17%) orientations of the reacting fragments were

identified, accompanied by a polycyclic compound that could not be fully characterized and might be derived, when compared with the reactivity of **25**, from further rearrangements of the putative *Re-endo* diastereomer.

Computational studies on the IMDA reaction of model systems

DFT calculations at the ωB97XD/Def2SVP level[36] using the Gaussian 09 suite of programs[37] of the non-conjugated tetraenal model system **I** (Scheme 6) lacking the trihydroxylated side chain of nahuoic acid **1a** in toluene or MeOH as solvent were carried out in order to analyze and thus justify the diastereoselectivity of the IMDA reaction. Conformational analysis of model reactant **I** indicates s-*cis*,s-*cis* to be the most stable conformer as it reduces the destabilizing interactions between the methyl substituents of the formal 1,3,5,6-tetramethylhexatriene fragment, whereas conformers showing a single bond rotation of these Csp^2–Csp^2 connections are destabilized by only 0.5–0.7 kcal mol^{-1}, and the s-*trans*,s-*trans* extended conformation is destabilized by 2.3 kcal mol^{-1} (Scheme 6A). Further destabilization was expected for the model reactant to adapt to the folded conformation required for the IMDA reaction. The energy values computed for the reacting conformations (Scheme 6B) vary between 2.7 and 5.8 kcal mol^{-1} from the most stable extended s-*cis*,s-*cis* conformer of **I**.

All IMDA reactions were characterized as concerted but asynchronous cycloadditions, with the formed C3–C8 shorter than the C2–C11 bond length (ESI†). Although the lowest energy of activation ($\Delta G^{\#} = 30.5$ kcal mol^{-1}, Scheme 6B) was computed for the transition state leading to the *Si-exo* product **II** from the s-*cis*,s-*trans* conformer of **I** in the folded conformation (itself disfavored by 5.4 kcal mol^{-1}), those for the *Re-endo* and *Re-exo* transition states showed similar energy values ($\Delta G^{\#} = 30.7$ and 31.0 kcal mol^{-1}, respectively, Scheme 6B) and therefore the octahydronaphthalene diastereomers should also be present in the reaction mixture as IMDA reaction products. The IMDA *Re-endo* approach exhibited the highest energy of activation of the series ($\Delta G^{\#} = 33.0$ kcal mol^{-1}, Scheme 6B) despite being the less disfavored (by 2.7 kcal mol^{-1}) starting conformation. Therefore, the computational data confirms the lack of selectivity of the IMDA reaction under thermal reaction conditions for this system and provides a theoretically estimated diastereomeric ratio at 200 °C (39 : 25 : 33 dr *Si-exo* **35**/*Re-exo* **36**/*Re-endo* **37**) that is consistent with the experimental results.

To summarize, an efficient biogenetic approach to the acyclic pentaene fragment of nahuoic acid A was carried out, and the limitations were noted for the construction of the bicyclic octahydronaphthalene core using the IMDA reaction. However upon using Me_2AlCl to activate tetraenal model system **25** in CH_2Cl_2 at −78 °C for 24 h, a single diastereomer (*Re-endo* **37**) was obtained under thermal cyclization reaction conditions (BHT, *o*-xylene, 200 °C), and a mixture of three diastereomers (*Si-exo* **35**/*Re-exo* **36**/*Re-endo* **37** 40 : 40 : 20 dr) was generated, being the major components formed through the *exo* mode of cycloaddition of diene and dienophile (*exo*/*endo* ratio of *ca.* 3.76 : 1) with opposite facial selectivity. The IMDA reaction catalyzed by the bulky Lewis acid $B(C_6F_5)_3$ provided these octahydronaphthalenes with lower diastereoselectivity (2.5 : 1 *exo*/*endo* ratio), and moreover this protocol could not be extended to the pentaenal model system **34b**, which underwent the IMDA reaction under thermal reaction conditions to afford a mixture of the *Si-exo* **40b** and *Re-exo* **39b** octahydronaphthalenes in a *ca.* 1 : 1 ratio.

Total synthesis of nahuoic acid A (1a)

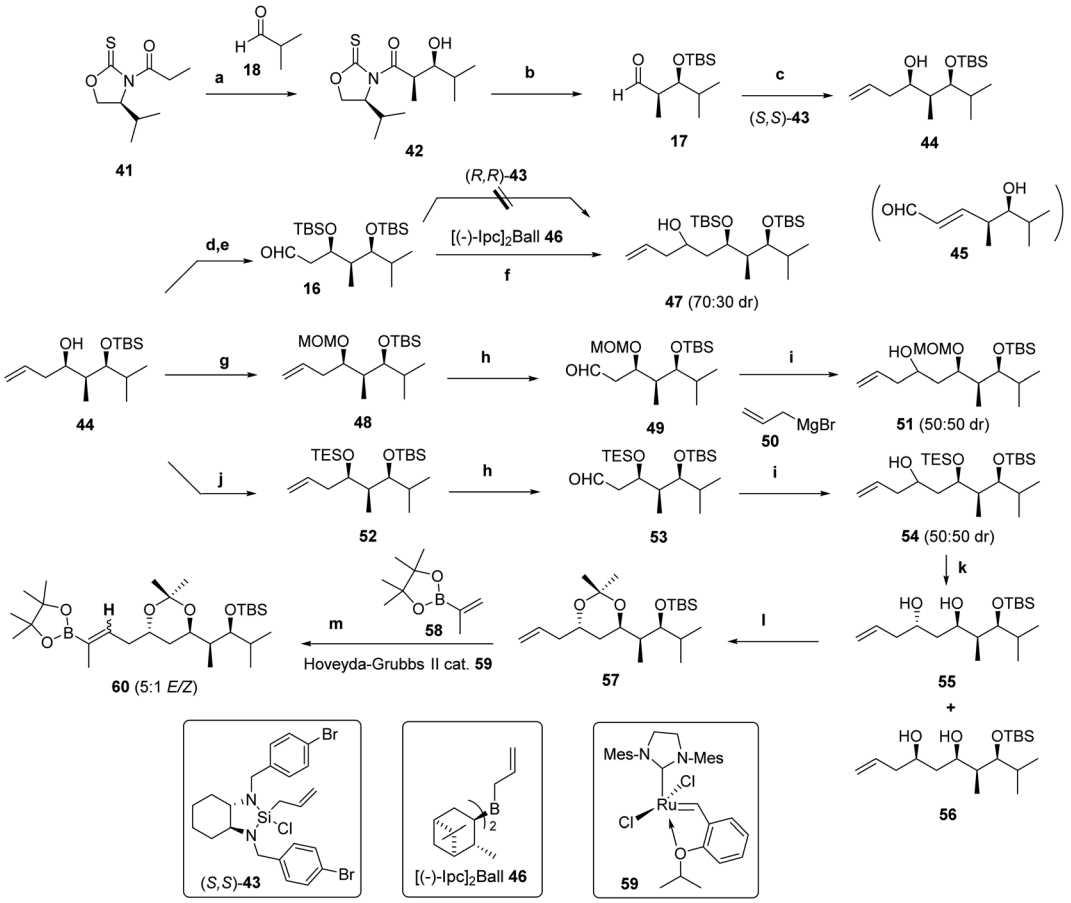
Since iodotetraenal **33b** (Scheme 4) contains the appropriate fragment to generate the octahydronaphthalene core of nahouic acid A (**1a**) through the IMDA reaction, the stereoselective synthesis of the trihydroxylated side chain with four stereocenters present in natural products **1a–1d** was addressed, as summarized in Scheme 3.

The synthesis started from the aldol reaction of the enolates derived from *N*-acyloxazolidine-2-thione **41** (ref. 38) containing Nagao's auxiliary[39] and isobutyraldehyde **18**. The combination of $TiCl_4$ and DIPEA at −78 °C (ref. 40) afforded the *syn "non-Evans" aldol* product **42** in 80% yield with very high diastereoselectivity.[41] Transformation of **42** into the corresponding aldehyde **17** involved the formation of the Weinreb amide [Me(OMe)HN·HCl, imidazole],[42] protection of the alcohol as silyl ether (TBDMSOTf, 2,6-lutidine) and reduction with DIBAL-H (THF, −78 °C), which resulted in an overall 71% yield (Scheme 7).

Allylation of **17** using the optimized protocol of Leighton *et al.*[43] with (*S*,*S*)-**43** and $Sc(OTf)_3$ at 0 °C for 24 h afforded the homoallylic alcohol **44** in quantitative yield as a single diastereomer.[44] Despite this promising result, further allylation of aldehyde **16**, which was obtained by protection of **44** as silyl ether and ozonolysis (upon treatment first with O_3 in CH_2Cl_2 at −78 °C for 1 min and then with PPh_3) with the enantiomeric reagent (*R*,*R*)-**43** (not shown) was unsuccessful and mixtures of compounds were obtained, from which the deprotected and dehydrated derivative of the homoallylic alcohol reactant (compound **45**) could be identified (Scheme 7). No further improvement was observed upon modification of the work-up procedure using a saturated aqueous solution of $NaHCO_3$ instead of TBAF, or freshly-opened bottles of the reagent. Conformational effects likely play a role in the reactivity of this intermediate,[45] given the formal destabilizing 1,3-*syn*-pentane-type interactions[46] between the methyl groups and also between the two silyloxy substituents (see the ESI†)

When using instead the allyl bis-isopinocampheylborane [(−)$Ipc_2BCH_2CH{=}CH_2$ or (−)-Ipc_2Ball **46**],[47] itself prepared by treatment of (−)-Ipc_2BCl [derived from hydroboration of (+)-α-pinene with chloroborane etherate ($H_2BCl{\cdot}OEt_2$)] with allylmagnesium bromide,[48] the resulting homoallylic alcohol **47** (Scheme 7) was obtained from **16** in high yield (90%) but, unfortunately, as a mixture of diastereomers (70 : 30 dr).

Considering that the size of the protecting group might interfere with the diastereoselective allylation, alternative protecting groups were assayed. The *p*-methoxybenzyl ether, which could eventually be further modified by oxidation with DDQ in order to achieve the double protection of the 1,3-diol,[49] was first

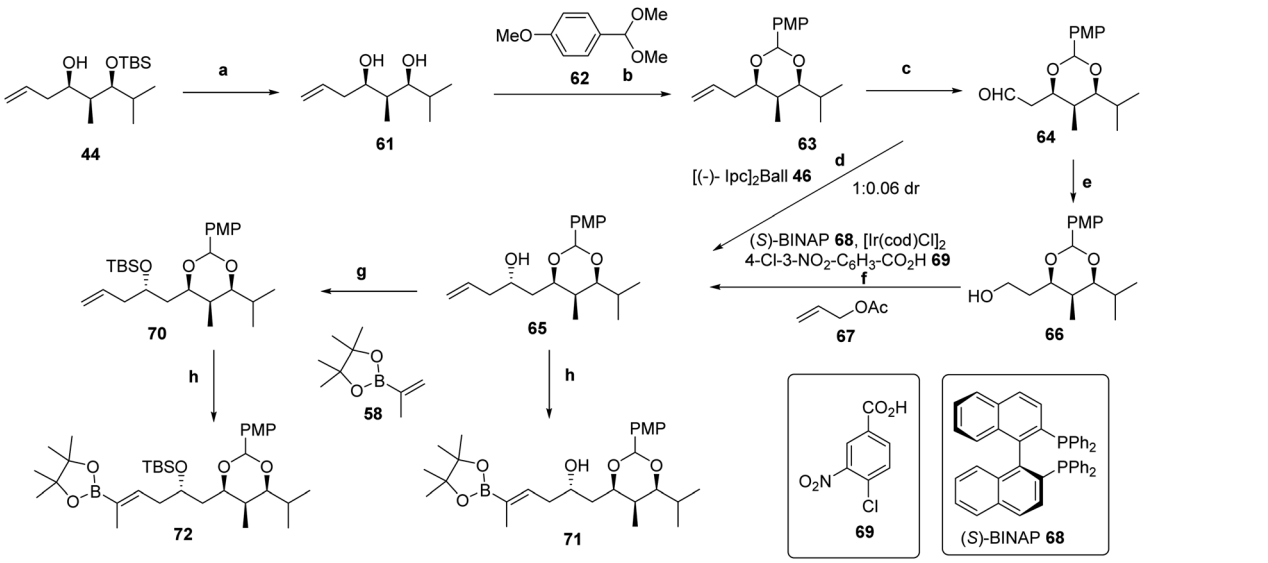


Scheme 7 Reagents and reaction conditions: (a) $TiCl_4$, i-Pr_2NEt, CH_2Cl_2, 0 to −78 °C, 3 h (80%). (b(i)) Me(OMe)NH·HCl, imidazole, CH_2Cl_2, 25 °C, 24 h. (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h. (iii) DIBAL-H, THF, −78 °C, 6 h (71%, three steps); (c) (*S*,*S*)-**43**, $Sc(OTf)_3$, CH_2Cl_2, 0 to 25 °C, 22 h (99%). (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h (94%). (e(i)) O_3, CH_2Cl_2, −78 °C, 1 min. (ii) PPh_3, 25 °C, 1 h (**16**, 92%). (f) (−)-Ipc_2Ball **46**, Et_2O, −78 to −30 °C, 5 h, 90% (70 : 30 dr). (g) MOMCl, DIPEA, CH_2Cl_2, 25 °C, 22 h (85%). (h(i)) O_3, CH_2Cl_2, −78 °C, 3 min. (ii) PPh_3, 25 °C, 1 h (94% for **49**; 81% for **53**). (i) Allyl magnesium bromide **50**, THF, 0 to 25 °C, 6 h (70% for **51**, 76% for **54**, 50 : 50 dr). (j) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h (86%). (k) AcOH/H_2O (4 : 1 v/v), THF, 25 °C, 12 h (99%). (l) 2,2-DMP, PPTS, CH_2Cl_2, 25 °C, 10 h (86%). (m) **58**, Hoveyda–Grubbs II cat. **59**, CH_2Cl_2, reflux, 17.5 h (5 : 1 *E*/*Z* ratio, 60%).

selected. However, using a variety of reaction conditions,[50] from the more classical NaH, *p*-methoxybenzyl chloride and *n*-Bu_4NI to modified protocols changing the base to KH and adding DMF,[51] led to complex mixtures of silyl ethers resulting from *trans*-silylation reactions of reactant **44**. Treatment with the trichloroacetimidate derivative $PMBOC(NH)CCl_3$ and $Cu(OTf)_2$ instead led to the recovery of the substrate. Attempts to alternatively protect the Weinreb amide intermediate as a *p*-methoxybenzyl ether were also unsuccessful.

Although benzylation of the homoallylic alcohol was feasible (but in low yields), the subsequent ozonolysis led to product degradation. Lastly, protection as the mixed acetal upon treatment with MOMCl (DIPEA and CH_2Cl_2)[52] followed by ozonolysis of **48** as described above for **16** afforded **49** in a combined 80% yield (Scheme 7). Using Leighton's reagent (*R*,*R*)-**43** (Scheme 7)[43] the outcome was unfortunately the same as obtained with the silyl ether. The allylation with allyltributylstannane mediated by $Ti(O^iPr)_4$ and (*S*)-BINOL following the protocol described by Keck *et al.*,[53] did not take place. The same result was observed using (−)-Ipc_2Ball **46** (Scheme 7).[54] However, the allylation of **49** with an excess of allylmagnesium bromide **50** in THF[55] did afford the homoallylic alcohol **51** in 76% yield but unfortunately as a 50 : 50 mixture of diastereomers (Scheme 7). The relative and absolute configurations of **51** were determined by the analysis of the ^{13}C-NMR chemical shifts of the corresponding acetal derivatives following Rychnovsky's protocol.[2] The same approach was adopted for the triethylsilyl ether **53**, which was prepared from monoprotected 1,3-diol **44** following a similar sequence.[56] For characterization purposes, deprotection of an equimolar mixture of allylic alcohol **54** with AcOH and H_2O (4 : 1 v/v) in THF for 12 h (ref. 57) afforded diastereomeric diols **55** and **56**, which were separated and treated with 2,2-dimethoxypropane and PPTS (Scheme 8).[58] The structure of the *anti* diastereomer **55** could be easily confirmed based on the similar ^{13}C-NMR chemical shift values measured for the methyl groups of the acetal.[2]

Cross-metathesis reaction of *anti*-**55** and propenylpinacolboronate **57** using Hoveyda–Grubbs 2nd generation catalyst **59**,[59a,b] in CH_2Cl_2 under reflux conditions[59c] led to a 5 : 1 *E*/*Z* mixture of trisubstituted alkenylpinacolboronate isomer **60** in



Scheme 8 Reagents and reaction conditions: (a) TBAF, THF, 0 to 25 °C, 4 h, 99%. (b) *p*-Anisaldehyde dimethylacetal **62**, CSA, CH_2Cl_2, 25 °C, 4 h, 86%. (c) $K_2OsO_2(OH)_4$, $NaIO_4$, 2,6-lutidine, 1,4-dioxane, H_2O, 25 °C, 3 h, 98%. (d) [(−)-Ipc$_2$]Ball **46**, Et_2O, −78 °C, 4 h, 86%. (e) $NaBH_4$, MeOH, −10 °C, 30 min, 99%. (f) **67**, (*S*)-BINAP **68**, $[Ir(cod)Cl]_2$, 4-Cl,3-NO_2-$C_6H_3CO_2H$ **69**, Cs_2CO_3, THF, 100 °C, 40 h, 82%. (g) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 h, 99%; (h) **65** or **70**, Hoveyda–Grubbs II **59** (cat.), degassed CH_2Cl_2, 40 °C, 24 h (70% for **71**; 57% for **72**).

60% yield (Scheme 7). Given the lack of stereocontrol in the last two C–C bond-formation steps, the sequence was reconsidered using alternative protecting groups.

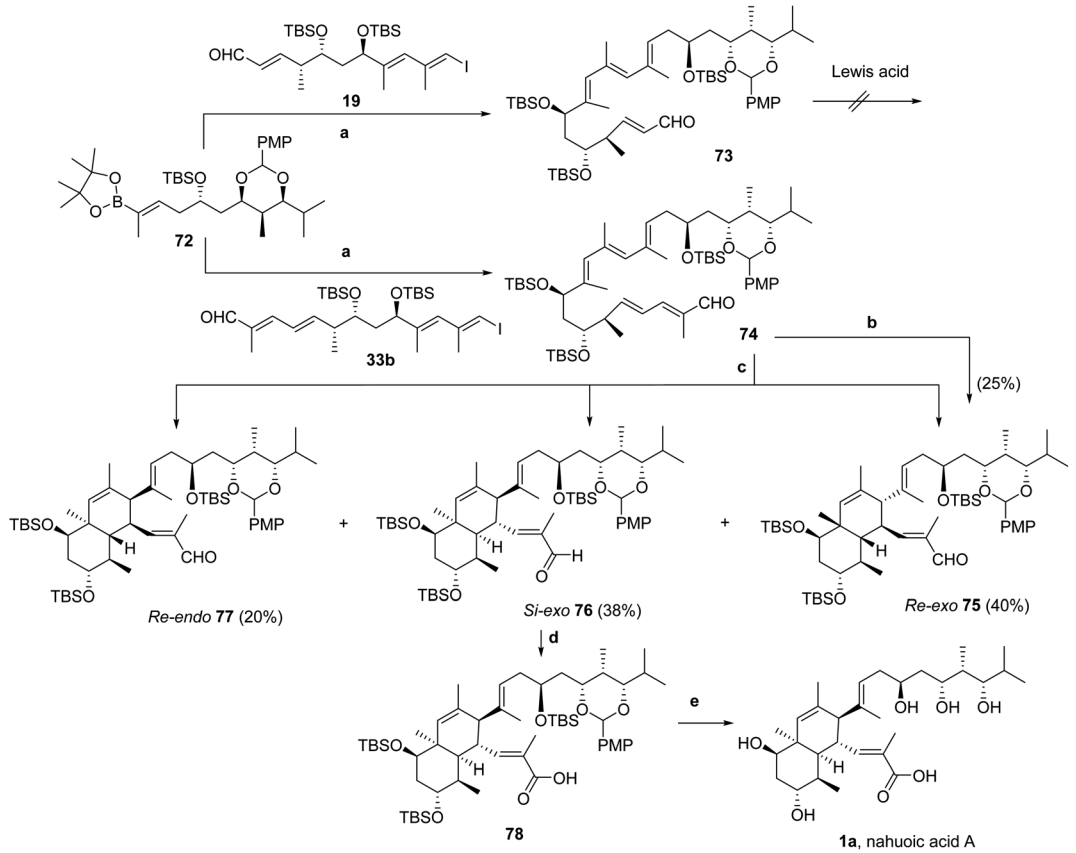
Straightforward deprotection of the silyl ether of **44** with TBAF (99% yield) was followed by protection of the *syn*-1,3-diol **61** as a cyclic acetal.[60] Since the anisylidene protecting group is *ca.* 10 times more labile to acid than isopropylidene or benzylidene counterparts, dioxolane **63** was chosen to protect the *syn*-1,3-diol **61**, and the process was carried out using *p*-anisaldehyde dimethylacetal **62** and camphorsulfonic acid.[61] Oxidative cleavage through a modified procedure,[62] involving treatment with catalytic OsO_4, 2,6-lutidine and $NaIO_4$, generated aldehyde **64** in 98% yield (Scheme 9). Using Antilla's method for allylboration of aldehydes using (*R*)-TRIP-PA and the allyltetramethyldioxaborolane reagents,[63] a *ca.* 1 : 1 mixture of diastereomers was obtained. The result was comparable to that obtained using allyltributylstannane and $MgBr_2 \cdot Et_2O$. Alternative methods for the allylation of aldehyde **64** which proved to be inefficient or capricious, were Leighton's protocol,[43b] Keck's Ti(OiPr)$_4$-(*S*)-BINOL system,[53] and Brown's (−)-Ipc$_2$Ball generated *in situ* from (−)-Ipc$_2$BCl and allyl magnesium bromide.[62] However, when recently purchased [(−)-(Ipc$_2$)]Ball reagent **46** was used, the desired homoallylic alcohol **65** was obtained in 86% yield accompanied by very minor amounts of the diastereomer (1 : 0.06 dr). Despite the success, the instability of the reagent and its use in stoichiometric amounts made necessary to search for a more robust and efficient procedure.

To this end, we focused on Krische's enantioselective carbonyl allylation *via* transfer hydrogenation coupling with allylic acetates catalyzed by chiral non-racemic iridium complexes generated from $[Ir(cod)Cl]_2$ and an enantiopure biphosphine ligand.[64] Following this procedure, alcohol **66**, which was efficiently generated upon reduction of aldehyde **64** with $NaBH_4$ in MeOH at −10 °C for 30 min,[65] was treated with allyl acetate **67**, (*S*)-BINAP **68**, $[Ir(cod)Cl]_2$, 4-chloro-3-nitrobenzoic acid **69** and Cs_2CO_3 at 100 °C for 40 h (ref. 66) to provide homoallylic alcohol **65** as a single diastereomer in 82% yield (Scheme 8).

Cross-metathesis as described above using Hoveyda–Grubbs 2nd generation catalyst **59** (5 mol%) and excess (5 equiv.) of isopropenyldioxaborolane **58** in refluxing benzene for 18 h[67] led to the desired unsaturated alkenylpinacolboronate **71** although in a disappointing 23% yield, together with the dimer and other unidentified by-products. However, adopting the variant[68] based on the addition of 10 equivalents of boronate **58** to a solution of **65** in dichloromethane and portionwise (3×) addition of the catalyst (5% + 2.5% + 2.5%) with removal of the also generated ethylene from the frozen flask under high vacuum conditions, the yield of **71** could be increased to 70% (Scheme 8).

The generated δ-hydroxyboronic acid **71** was used in the Suzuki–Miyaura cross-coupling reaction[23] with dienyl iodide **15** (Scheme 2), promoted by $Pd(PPh_3)_4$ as the catalyst and 10% aqueous TlOH in THF at room temperature, but the yields of the resulting triene were lower than 30%. In turn, protection of the free alcohol of **65** as a silyl ether in quantitative yield using TBDMSOTf and 2,6-lutidine in CH_2Cl_2 allowed us to carry out the same cross-metathesis connection of **58** with **70** catalyzed by **59** to afford internal alkenyl pinacolboronate **72** in 57% yield (Scheme 8).

Suzuki–Miyaura cross-coupling[23] of components **72** and **19** (Scheme 2) was in this case highly effective, and non-conjugated tetraenal **73** was obtained in 93% yield (Scheme 9). Non-conjugated pentaenal **74** was likewise prepared by Suzuki–Miyaura cross-coupling[23] of **72** and **33b** in 86% yield (Scheme 9).



Scheme 9 Reagents and reaction conditions: (a) $Pd(PPh_3)_4$, 10% aq. TlOH, THF, 25 °C, 3 h (93% for **73**; 86% for **74**). (b) BHT, *o*-xylene, 200 °C, 18 h (25% for *Re-exo* **75**). (c) $Eu(fod)_3$, BHT, toluene, 160 °C, 16 h or CD_3OD, BHT, 170 °C, 14 h (40% for *Re-exo* **75**; 38% for *Si-exo* **76**; 20% for *Re-endo* **77**). (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*BuOH/H_2O, 25 °C, 12 h, 84%. (e) 4 M HCl, THF, 25 °C, 64 h, 22%.

The IMDA reaction[22] was first attempted with non-conjugated tetraenal **73** under Lewis acid-catalyzed conditions. However, all trials led to the recovery of **73** when using Me_2AlCl in toluene at low temperatures (−78 to −40 °C)[30] or $B(C_6F_5)_3$ in CH_2Cl_2 (with powdered 4 Å MS) at −10 °C.[31] Product degradation and formation of unidentified mixtures of by-products were noticed upon increasing the reaction temperature following these protocols to either −10 °C or 23 °C, respectively.

Using instead the non-conjugated pentaenal **74**, IMDA cycloaddition (Scheme 9) was promoted by heating the solution in *o*-xylene at 200 °C for 18 h (longer reaction periods were detrimental to the stability of the products and extensive decomposition was also noted). Purification by HPLC (Synergi MAX-RP column, C18-silica gel, 4 μm, 250 × 4.6 mm; MeOH, flow rate = 2 mL min^{-1}) allowed us to characterize the major product (t_R = 19 min), obtained in 25% yield, as the cycloadduct *Re-exo* **75**, by analysis of ^{1}H- and ^{13}C-NMR spectra in CD_2Cl_2 solution, DEPT data, NOE effects, and two-dimensional NMR experiments (HSQC, HMBC, COSY, DQF-COSY, and TOCSY1D) as well as MS data. Additional reaction products (10–15% yield) could not be identified, but the NMR data resembled those of *Re-exo* **75**.

Moreover, computational studies (see the ESI†) predicted a reduction in activation energies for the IMDA reaction of the *s-trans* conformer (up to $\Delta\Delta G^{\ddagger} \approx 4$ kcal mol^{-1}), when using MeOH as solvent relative to toluene, and a greater selectivity for formation of octahydronaphthalenes through the *Si-exo* relative to the *Re-endo* ($\Delta\Delta G^{\ddagger} \approx 1.8$ kcal mol^{-1}) approach. Monitoring the IMDA reaction process by ^{1}H-NMR spectroscopy using solutions of **74** in CD_3OD with BHT as a radical scavenger allowed us to confirm the prediction, since the reaction was completed after heating at 170 °C for 14 h. Separation of the products by HPLC as described above allowed us to identify, in order of elution, the *Re-exo* **75** (40% yield), *Si-exo* **76** (38% yield) and *Re-endo* **77** (20% yield) diastereomers in excellent overall yield. A similar result was obtained upon alternatively heating solutions of **74** in toluene-d_8 with BHT using a weak Lewis acid [$Eu(fod)_3$, Resolve-Al®] as the catalyst at 160 °C for 16 h (Scheme 9).

Therefore, the use of the entire pentaenal **74** under the IMDA thermal cyclization reaction conditions allowed us to improve the *exo*/*endo* ratio to 4 : 1 (*cf.* 3.76 : 1 in the case of **25**, Scheme 5) when compared to the results obtained (2.5 : 1) with the bulky Lewis acid $B(C_6F_5)_3$ for model system **34b** (Scheme 5). In addition, the results agree with the computational predictions on the tetraenal model system under thermal conditions.

The *Si-exo* diastereomer **76** was oxidized under the Pinnick–Lindgren reaction conditions[69] modified by adding THF in addition to ^{t}BuOH/H_2O as the solvent mixture,[70] which afforded

carboxylic acid **78** in 80% yield after 12 h stirring (Scheme 9). Being acid-sensitive protecting groups, further treatment of solutions of **78** in THF with 4 N HCl at ambient temperature for 72 h led to overall deprotection.[71] Work-up using $NaHCO_3$ followed by the addition of 1 M TFA until pH ≈ 1 and freeze-drying provided a solid that was dissolved in ethyl acetate, filtered with Celite®, and evaporated to dryness. Finally, HPLC purification of the residue (Synergi MAX-RP column, C12-silica gel, 4 μm, 250 × 4.6 mm; linear gradient elution from 30% MeCN in water to 100% MeCN over 30 min, with a flow rate of 2.5 mL min^{-1}) provided nahuoic acid A (**1a**) in an overall 22% yield (Scheme 9). The ^{1}H-NMR data matched those previously reported for the natural product.[1a]

C Conclusions

To summarize, the bioinspired synthesis of nahuoic acid A (**1a**) was achieved using the IMDA reaction of non-conjugated pentaenal **74** to construct the octahydronaphthalene core structure of the natural product. The synthesis of pentaenal **74** made use of Suzuki cross-coupling of a non-conjugated iodotetraenal **33b** and trisubstituted alkenylboronate **72**, themselves prepared through enantio- and diastereoselective reactions including the Evans aldol condensation reaction, and a sequence of the Leighton and Krische allylation reactions, as well as the cross-metathesis for the generation of the alkenylboronate. IMDA reaction upon heating solutions of **74** in CD_3OD with BHT as the radical scavenger at 170 °C for 14 h afforded a mixture of three diastereomers (*Re-exo*, *Si-exo* and *Re-endo*) in a 2 : 2 : 1 ratio and high yield, favoring the *exo* mode of cycloaddition with one stereoisomer (*Si-exo*) showing the relative and absolute configurations present in nahuoic acid A (**1a**). The preference for the *exo*-mode of cycloaddition in an uncatalyzed thermal process has been computationally predicted. By contrast, catalysis by Me_2AlCl at −40 °C of model tetraenal **25** was highly selective for the *trans*-fused angularly-methylated octahydronaphthalene model fragment **37** corresponding to the *Re-endo* mode of cycloaddition.

Given the reactivity of the synthetic non-conjugated pentaenal **74**, it is tempting to suggest that the putative DNAse enzyme of *Streptomyces* sp. (isolate RJA2928) might be providing an active site environment that allows us to select the conformation of the unprotected and natural component leading to the *cis* decalin stereoisomer of nahuoic acid A (**1a**).[24e,f,72] In line with this assumption, recent studies by Houk and co-workers on a model system of an electrocyclic reaction catalyzed by the MycB protein revealed that although the activation free energy for the spontaneous reaction (catalyzed by *p*-cresol) was lower for the *cis*-decalin *exo* adduct, the model MycB-catalyzed reaction, likewise a synchronous and concerted process, led to the *trans*-decalin through the *endo* transition state approach.[24f,73]

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Conceptualization: A. R. de L.; funding acquisition: A. R. de L. and R. A.; methodology: A. R. de L. and R. A.; investigation: L. G., P. M., and P. V.; methodology: A. R. de L. and R. A.; project administration: A. R. de L. and R. A.; supervision: A. R. de L. and R. A.; computations: P. V. and R. A.; visualization: P. V. and R. A.; writing-original draft: A. R. de L.; writing, review and editing: L. G.; P. M., P. V.; R. A., and A. R. de L.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) D. E. Williams, D. S. Dalisay, F. Li, J. Amphlett, W. Maneerat, M. A. G. Chavez, Y. A. Wang, T. Matainaho, W. Yu, P. J. Brown, C. H. Arrowsmith, M. Vedadi and R. J. Andersen, *Org. Lett.*, 2013, **15**, 414–417; (*b*) D. E. Williams and R. J. Andersen, *Nat. Prod. Rep.*, 2020, **37**, 617–633.

2 S. D. Rychnovsky, B. Rogers and G. Yang, *J. Org. Chem.*, 1993, **58**, 3511–3515.

3 (*a*) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512–519; (*b*) T. R. Hoye, C. S. Jeffrey and F. Shao, *Nat. Protoc.*, 2007, **2**, 2451–2458.

4 (*a*) X.-H. Nong, X.-Y. Zhang, X.-Y. Xu, J. Wang and S.-H. Qi, *J. Nat. Prod.*, 2016, **79**, 141–148. None of these natural products (Fig. 1) showed inhibitory activity against acetylcholinesterase, cytotoxicity towards the H1975, K562, BGC 823, MCF-7, HL-60, and Huh-7 cancer cell lines, antibacterial activity against *Staphylococcus aureus* and *Shewanella oneidensis* MR-1 or antibiofilm activity against *S. aurueus*.(*b*) D. E. Williams, F. Izard, S. Arnould, D. S. Dalisay, C. Tantapakul, W. Maneerat, T. Matainaho, E. Julien and R. J. Andersen, *J. Org. Chem.*, 2016, **81**, 1324–1332.

5 Q. Liu, Y. Deng and A. B. Smith III, *J. Am. Chem. Soc.*, 2017, **139**, 13668–13671.

6 A. Ma, W. Yu, Y. Xiong, K. V. Butler, P. J. Brown and J. Jin, *MedChemComm*, 2014, **5**, 1892–1898.

7 (*a*) H. ú. Kaniskan, K. D. Konze and J. Jin, *J. Med. Chem.*, 2015, **58**, 1596–1629; (*b*) M. Schapira, *Cell Chem. Biol.*, 2016, **23**, 1067–1076; (*c*) Z. A. Wang and W. R. Liu, *Chem.–Eur. J.*, 2017, **23**, 11732–11737; (*d*) V. Veschi, Z. Liu,

T. C. Voss, L. Ozbun, B. Gryder, C. Yan, Y. Hu, A. Ma, J. Jin, S. J. Mazur, N. Lam, B. K. Souza, G. Giannini, G. L. Hager, C. H. Arrowsmith, J. Khan, E. Appella and C. J. Thiele, *Cancer Cell*, 2017, **31**, 50–63; (*e*) M. Luo, *Chem. Rev.*, 2018, **118**, 6656–6705; (*f*) S. Chen, K. Kapilashrami, C. Senevirathne, Z. Wang, J. Wang, J. A. Linscott and M. Luo, *J. Am. Chem. Soc.*, 2019, **141**, 8064–8067.

8 (*a*) S. M. Kooistra and K. Helin, *Nat. Rev. Mol. Cell Biol.*, 2012, **13**, 297–311; (*b*) J. W. Hojfeldt, K. Agger and K. Helin, *Nat. Rev. Drug Discovery*, 2013, **12**, 917–930.

9 (*a*) J. C. Black, C. Van Rechem and J. R. Whetstine, *Mol. Cell*, 2012, **48**, 491–507; (*b*) L. Morera, M. Lübbert and M. Jung, *Clin. Epigenet.*, 2016, **8**, 57.

10 J. A. Linscott, K. Kapilashrami, Z. Wang, C. Senevirathne, I. R. Bothwell, G. Blum and M. Luo, *Proc. Natl. Acad. Sci. U. S. A.*, 2016, **113**, E8369–E8378.

11 (*a*) X. Cheng, R. E. Collins and X. Zhang, *Annu. Rev. Biophys. Biomol. Struct.*, 2005, **34**, 267–294; (*b*) M. B. Poulin, J. L. Schneck, R. E. Matico, P. J. McDevitt, M. J. Huddleston, W. Hou, N. W. Johnson, S. H. Thrall, T. D. Meek and V. L. Schramm, *Proc. Natl. Acad. Sci. U. S. A.*, 2016, **113**, 1197–1201.

12 (*a*) M. Takawa, H.-S. Cho, S. Hayami, G. Toyokawa, M. Kogure, Y. Yamane, Y. Iwai, K. Maejima, K. Ueda, A. Masuda, N. Dohmae, H. I. Field, T. Tsunoda, T. Kobayashi, T. Akasu, M. Sugiyama, S.-i. Ohnuma, Y. Atomi, B. A. J. Ponder, Y. Nakamura and R. Hamamoto, *Cancer Res.*, 2012, **72**, 3217–3227; (*b*) C. Milite, A. Feoli, M. Viviano, D. Rescigno, A. Mai, S. Castellano and G. Sbardella, *ChemMedChem*, 2016, **11**, 1680–1685.

13 J. Fang, Q. Feng, C. S. Ketel, H. Wang, R. Cao, L. Xia, H. Erdjument-Bromage, P. Tempst, J. A. Simon and Y. Zhang, *Curr. Biol.*, 2002, **12**, 1086–1099.

14 X. Shi, I. Kachirskaia, H. Yamaguchi, L. E. West, H. Wen, E. W. Wang, S. Dutta, E. Appella and O. Gozani, *Mol. Cell*, 2007, **27**, 636–646.

15 F. Yang, L. Sun, Q. Li, X. Han, L. Lei, H. Zhang and Y. Shang, *EMBO J.*, 2012, **31**, 110–123.

16 S. Jørgensen, I. Elvers, M. B. Trelle, T. Menzel, M. Eskildsen, O. N. Jensen, T. Helleday, K. Helin and C. S. Sørensen, *J. Cell Biol.*, 2007, **179**, 1337–1345.

17 K. W. Kuntz, J. E. Campbell, H. Keilhack, R. M. Pollock, S. K. Knutson, M. Porter-Scott, V. M. Richon, C. J. Sneeringer, T. J. Wigle, C. J. Allain, C. R. Majer, M. P. Moyer, R. A. Copeland and R. Chesworth, *J. Med. Chem.*, 2016, **59**, 1556–1564.

18 (*a*) C. Pérez-Balado, P. Rodríguez-Graña, A. Nebiosso, A. Minichiello, M. Miceli, L. Altucci and A. R. de Lera, *J. Med. Chem.*, 2007, **50**, 2497–2505; (*b*) J. A. Souto, E. Vaz, I. Lepore, A.-C. Pöppler, G. Franci, R. Álvarez, L. Altucci and Á. R. de Lera, *J. Med. Chem.*, 2010, **53**, 4654–4667; (*c*) J. García, G. Franci, R. Pereira, R. Benedetti, A. Nebbioso, F. Rodríguez-Barrios, H. Gronemeyer, L. Altucci and A. R. de Lera, *Bioorg. Med. Chem.*, 2011, **19**, 3637–3649; (*d*) P. García-Domínguez, I. Lepore, C. Erb, H. Gronemeyer, L. Altucci, R. Álvarez and A. R. de Lera, *Org. Biomol. Chem.*, 2011, 6979–6987.

19 L. Guillade, A. B. Gonzalez-Perez and A. R. de Lera, *Org. Biomol. Chem.*, 2017, **15**, 7430–7438.

20 Y. Deng and A. B. Smith, *Acc. Chem. Res.*, 2020, **53**, 988–1000.

21 (*a*) H. A. Reichard and G. C. Micalizio, *Angew. Chem., Int. Ed.*, 2007, **46**, 1440–1443; (*b*) G. C. Micalizio and S. B. Hale, *Acc. Chem. Res.*, 2015, **48**, 663–673; (*c*) N. F. O'Rourke, M. J. Kier and G. C. Micalizio, *Tetrahedron*, 2016, **72**, 7093–7123.

22 (*a*) W. R. Roush, in *Comprehensive Organic Synthesis*, ed. I. Fleming, B. M. Trost and L. A. Paquette, Pergamon Press, Oxford, 1991, ch. 4.4, vol. 5, pp. 513–550; (*b*) K.-i. Takao, R. Munakata and K.-i. Tadano, *Chem. Rev.*, 2005, **105**, 4779–4807; (*c*) M. Juhl and D. Tanner, *Chem. Soc. Rev.*, 2009, **38**, 2983–2992; (*d*) M. M. Heravi and V. F. Vavsari, *RSC Adv.*, 2015, **5**, 50890–50912.

23 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*b*) A. Suzuki, *Angew. Chem., Int. Ed.*, 2011, **50**, 6722–6737.

24 (*a*) E. M. Stocking and R. M. Williams, *Angew. Chem., Int. Ed.*, 2003, **42**, 3078–3115; (*b*) K. Klas, S. Tsukamoto, D. H. Sherman and R. M. Williams, *J. Org. Chem.*, 2015, **80**, 11672–11685; (*c*) A. Minami and H. Oikawa, *J. Antibiot.*, 2016, **69**, 500–506; (*d*) T. Hashimoto and T. Kuzuyama, *Curr. Opin. Chem. Biol.*, 2016, **35**, 117–123; (*e*) M. J. Byrne, N. R. Lees, L.-C. Han, M. W. van der Kamp, A. J. Mulholland, J. E. M. Stach, C. L. Willis and P. R. Race, *J. Am. Chem. Soc.*, 2016, **138**, 6095–6098; (*f*) L. Li, P. Yu, M.-C. Tang, Y. Zou, S.-S. Gao, Y.-S. Hung, M. Zhao, K. Watanabe, K. N. Houk and Y. Tang, *J. Am. Chem. Soc.*, 2016, **138**, 15837–15840.

25 (*a*) D. Tan, C. S. Jamieson, M. Ohashi, M.-C. Tang, K. N. Houk and Y. Tang, *J. Am. Chem. Soc.*, 2019, **141**, 769–773; (*b*) C. S. Jamieson, M. Ohashi, F. Liu, Y. Tang and K. N. Houk, *Nat. Prod. Rep.*, 2019, **36**, 698–713; (*c*) B.-s. Jeon, S.-A. Wang, M. W. Ruszczycky and H.-w. Liu, *Chem. Rev.*, 2017, **117**, 5367–5388; (*d*) B. R. Lichman, S. E. O'Connor and H. Kries, *Chem.–Eur. J.*, 2019, **25**, 6864–6877; (*e*) Z. Zhang, C. S. Jamieson, Y.-L. Zhao, D. Li, M. Ohashi, K. N. Houk and Y. Tang, *J. Am. Chem. Soc.*, 2019, **141**, 5659–5663; (*f*) C. T. Walsh and Y. Tang, *Natural Product Biosynthesis*. Chemical Logic and Enzymatic Machinery, Croydon, UK, 2017; (*g*) C. T. Walsh and Y. Tang, *Biochemistry*, 2018, **57**, 3087–3104; (*h*) C. T. Walsh and B. S. Moore, *Angew. Chem., Int. Ed.*, 2019, **58**, 6846–6879; (*i*) B. Zhang, K. B. Wang, W. Wang, X. Wang, F. Liu, J. Zhu, J. Shi, L. Y. Li, H. Han, K. Xu, H. Y. Qiao, X. Zhang, R. H. Jiao, K. N. Houk, Y. Liang, R. X. Tan and H. M. Ge, *Nature*, 2019, **568**, 122–126.

26 J. Uenishi, J.-M. Beau, R. W. Armstrong and Y. Kishi, *J. Am. Chem. Soc.*, 1987, **109**, 4756–4758.

27 A. L. Moure, R. Gómez Arrayás, D. J. Cárdenas, I. Alonso and J. C. Carretero, *J. Am. Chem. Soc.*, 2012, **134**, 7219–7222.

28 (*a*) K. C. Nicolaou, M. W. Härter, J. L. Gunzner and A. Nadin, *Liebigs Ann.*, 1997, **1997**, 1283–1301; (*b*) K. Kobayashi, K. Tanaka and H. Kogen, *Tetrahedron Lett.*, 2018, **59**, 568–582.

29 M. Ramanathan, C.-J. Tan, W.-J. Chang, H.-H. G. Tsai and D.-R. Hou, *Org. Biomol. Chem.*, 2013, **11**, 3846–3854.

30 J. P. Burke, M. Sabat, D. A. Iovan, W. H. Myers and J. J. Chruma, *Org. Lett.*, 2010, **12**, 3192–3195.
31 J.-H. Zhou, B. Jiang, F.-F. Meng, Y.-H. Xu and T.-P. Loh, *Org. Lett.*, 2015, **17**, 4432–4435.
32 *Ab initio* computations appear to be consistent with the lower energy cost associated with deformation of reagents to reach the transition state, where they get stabilized by a combination of stronger electrostatic interactions, dispersion forces and orbital interactions. In fact, non-covalent CH–F_{ortho} interactions in the activated model substrate were found to contribute to the stabilization of the *exo*-like transition state; see: D. Yepes, P. Pérez, P. Jaque and I. Fernández, *Org. Chem. Front.*, 2017, **4**, 1390–1399.
33 R. W. Hoffmann, *Angew. Chem., Int. Ed.*, 2001, **40**, 1411–1416.
34 P. Farfán, S. Gómez and A. Restrepo, *J. Org. Chem.*, 2019, **84**, 14644–14658.
35 (*a*) D. J. Ager, *J. Chem. Soc., Perkin Trans. 1*, 1986, 183–194; (*b*) F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297–3305; (*c*) F. Weigend, *Phys. Chem. Chem. Phys.*, 2006, **8**, 1057–1065.
36 J.-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 6615–6620.
37 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, in *Gaussian 09, Revision B.01*, Gaussian, Inc., Wallingford CT, 2009.
38 (*a*) M. Nerz-Stormes and E. R. Thornton, *J. Org. Chem.*, 1991, **56**, 2489–2498; (*b*) Y. Zhang and T. Sammakia, *Org. Lett.*, 2004, **6**, 3139–3141; (*c*) Y. Zhang, A. J. Phillips and T. Sammakia, *Org. Lett.*, 2004, **6**, 23–25.
39 Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto and E. Fujita, *J. Org. Chem.*, 1986, **51**, 2391–2393.
40 Á. González, J. Aiguadé, F. Urpí and J. Vilarrasa, *Tetrahedron Lett.*, 1996, **37**, 8949–8952.
41 (*a*) D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1990, **112**, 8215–8216; (*b*) M. T. Crimmins, B. W. King and E. A. Tabet, *J. Am. Chem. Soc.*, 1997, **119**, 7883–7884.
42 S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815–3818.
43 (*a*) J. W. A. Kinnaird, P. Y. Ng, K. Kubota, X. Wang and J. L. Leighton, *J. Am. Chem. Soc.*, 2002, **124**, 7920–7921; (*b*) H. Kim, S. Ho and J. L. Leighton, *J. Am. Chem. Soc.*, 2011, **133**, 6517–6520.
44 X. Zhang, K. N. Houk and J. L. Leighton, *Angew. Chem., Int. Ed.*, 2005, **44**, 938–941.
45 R. Chen, Y. Shen, S. Yang and Y. Zhang, *Angew. Chem., Int. Ed.*, 2020, **59**, 14198–14210.
46 G. Stork and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 1987, **109**, 1565–1567.
47 H. C. Brown and P. K. Jadhav, *J. Am. Chem. Soc.*, 1983, **105**, 2092–2093.
48 S. Das, D. Paul and R. K. Goswami, *Org. Lett.*, 2016, **18**, 1908–1911.
49 B. M. Trost, B. M. O'Boyle and D. Hund, *J. Am. Chem. Soc.*, 2009, **131**, 15061–15074.
50 L. Brewitz, J. Llaveria, A. Yada and A. Fürstner, *Chem.–Eur. J.*, 2013, **19**, 4532–4537.
51 M. W. Andersen, B. Hildebrandt, G. Dahmann and R. W. Hoffmann, *Chem. Ber.*, 1991, **124**, 2127–2139.
52 S. BouzBouz and J. Cossy, *Tetrahedron Lett.*, 2006, **47**, 901–904.
53 G. E. Keck, K. H. Tarbet and L. S. Geraci, *J. Am. Chem. Soc.*, 1993, **115**, 8467–8468.
54 P. Álvarez-Bercedo, J. Murga, M. Carda and J. A. Marco, *J. Org. Chem.*, 2006, **71**, 5766–5769.
55 M. C. Warner, G. A. Shevchenko, S. Jouda, K. Bogár and J.-E. Bäckvall, *Chem.–Eur. J.*, 2013, **19**, 13859–13864.
56 P. Wang, Y.-J. Kim, M. Navarro-Villalobos, B. D. Rohde and D. Y. Gin, *J. Am. Chem. Soc.*, 2005, **127**, 3256–3257.
57 K. Kobayashi, Y. Fujii, I. Hayakawa and H. Kigoshi, *Org. Lett.*, 2011, **13**, 900–903.
58 R. Perla, A. Ramisetti and R. Atla, *Tetrahedron Lett.*, 2016, **57**, 2100–2102.
59 (*a*) S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168–8179; (*b*) A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370; (*c*) C. Morrill, T. W. Funk and R. H. Grubbs, *Tetrahedron Lett.*, 2004, **45**, 7733–7736.
60 S. S. Dachavaram, K. B. Kalyankar and S. Das, *Tetrahedron Lett.*, 2014, **55**, 5629–5631.
61 P. Radha Krishna and M. Narsingam, *Synthesis*, 2007, 3627–3634.
62 R. G. Reddy, R. Venkateshwarlu, K. V. S. Ramakrishna, J. S. Yadav and D. K. Mohapatra, *J. Org. Chem.*, 2017, **82**, 1053–1063.
63 P. Jain and J. C. Antilla, *J. Am. Chem. Soc.*, 2010, **132**, 11884–11886.
64 I. S. Kim, M.-Y. Ngai and M. J. Krische, *J. Am. Chem. Soc.*, 2008, **130**, 14891–14899.
65 H. C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567–607.
66 J. Cui, M. Morita, O. Ohno, T. Kimura, T. Teruya, T. Watanabe, K. Suenaga and M. Shibasaki, *Chem.–Eur. J.*, 2017, **23**, 8500–8509.

67 M. Kretschmer, M. Dieckmann, P. Li, S. Rudolph, D. Herkommer, J. Troendlin and D. Menche, *Chem.–Eur. J.*, 2013, **19**, 15993–16018.
68 R. J. Armstrong, C. García-Ruiz, E. L. Myers and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2017, **56**, 786–790.
69 B. O. Lindgren and T. Nilsson, *Acta Chem. Scand.*, 1973, **27**, 888–890.
70 A. B. Smith III, K. Basu and T. Bosanac, *J. Am. Chem. Soc.*, 2007, **129**, 14872–14874.
71 (*a*) A. Arefolov and J. S. Panek, *J. Am. Chem. Soc.*, 2005, **127**, 5596–5603; (*b*) Y. Zhang, C. C. Arpin, A. J. Cullen, M. J. Mitton-Fry and T. Sammakia, *J. Org. Chem.*, 2011, **76**, 7641–7653.
72 K. Klas, S. Tsukamoto, D. H. Sherman and R. M. Williams, *J. Org. Chem.*, 2015, **80**, 11672–11685.
73 K. Black, P. Liu, L. Xu, C. Doubleday and K. N. Houk, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 12860–12865.