Cp2TiCl-catalyzed highly stereoselective intramolecular epoxide allylation using allyl carbonates

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ARTICLE TYPE

Cp_2TiCl-catalyzed highly stereoselective intramolecular epoxide allylation using allyl carbonates

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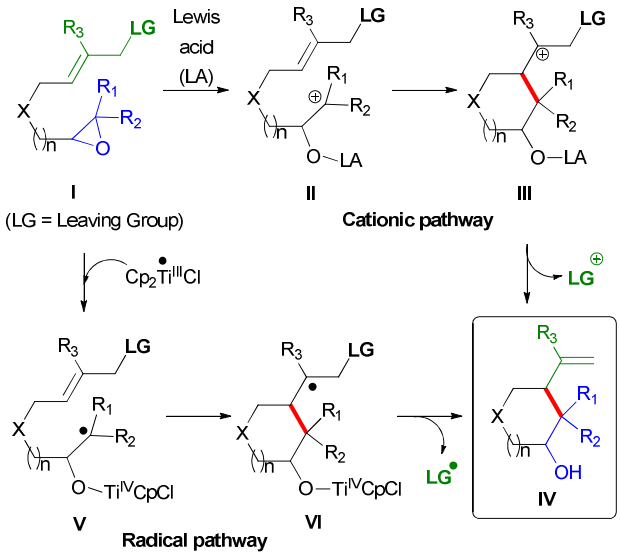
A useful method for the diastereoselective synthesis of vinyl substituted carbo- and heterocycles is described. Highly functionalized structures difficult to achieve by other methodologies are obtained in one single step by this procedure.

Epoxides are highly versatile functional groups in organic synthesis owing to the fact that their manipulation yields many attractive final products. Thus for example, diverse carbon nucleophiles such as Grignard and organolithium reagents or organocuprates, have been used in ring-opening reactions to install a new C-C bond.[1,2] The intramolecular version of this reaction would allow the preparation of different carbon and heterocycles with different size and functionality. Nevertheless, the synthesis of the suitable polyfunctionalized starting materials is not simple taking into account the chemical incompatibilities between the required reactive partners. In this context, neutral pronucleophiles like olefins or allylsilanes (**I**, LG = SiR_3, Scheme 1) are more convenient since they allow better control of the reaction and functional group compatibility.[3] A valuable advantage of the reactions of epoxides with allylsilanes, comparing with alkenes is their ability to stabilize β-carbocations (**III**, Scheme 1), and thereby controlling which carbon of the alkene is the nucleophilic carbon.[4] Moreover the allylsilane can control the direction of the final elimination acting as a good leaving group that stabilizes the generated positive charge (**IV**, Scheme 1). On the other hand, its main drawback is related to the electrophilic character of the reaction, which implies the use of Lewis acids, such as $TiCl_4$, and a strict control over the temperature. Another disadvantage of allylsilanes relative to simple alkenes is that extra synthetic steps are necessary owing to they are generally prepared from oxygenated-allyl groups. Therefore, the direct employment of allylic oxygenated functionalities in epoxide ring-opening reactions retaining the favourable characteristics of allyl silane analogues using very mild reaction conditions would represent an important advance in organic synthesis.

The limitation of this approach is that the corresponding β-carbocations (Scheme 1, **III**, LG = OCOR) would not be stabilized and the control of the direction of elimination would remain a challenge due to the lack of a carbocation stabilizing group and also a good leaving group. As a result, a cationic pathway can be discarded in this case, and an alternative reaction pathway based on carbon-centered radicals was considered. Cp_2TiCl[5]-mediated homolytic epoxide opening is a well-known reaction,[6–19] which has allowed many remarkable transformations, including a highly successful bioinspired approach to different natural products.[20–26] Epoxyallylcarboxylates **I** (LG = OCOR, Scheme 1) are expected to react with Cp_2TiCl, yielding radical intermediates type-**V**. After the homolytic opening of the epoxide, the β-titanoxy radical generated **V** would undergo further radical cyclization generating a carbon-centered radical **VI**. At this point, we expected that a oxygenated function in the β-position would act as good leaving group, thus directing the final elimination towards **IV** assisted by Cp_2TiCl as Lewis acid.[27,28] In fact, we had previously observed the Cp_2TiCl-mediated radical fragmentation of β-acetoxy alkyl radicals toward the corresponding alkenes.[21,29]

In this alternative radical pathway, Cp_2TiCl would play a crucial dual role for the intramolecular epoxide allylation with oxygenated-allyl groups: i) starting the reaction by homolytic opening of the oxirane ring and ii) controlling the final product obtained by radical fragmentation.



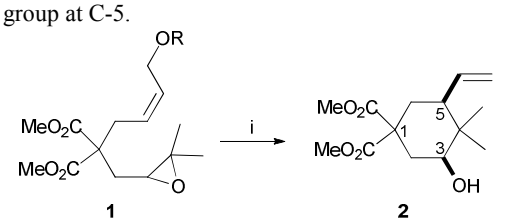
Scheme 1. Working hypothesis

Here we want to communicate that epoxides can formally be allylated intramolecularly in a highly diastereoselective manner under smooth reaction conditions using easily prepared and handled allylic carbonates as allylation reagents. This approach

also allows the preparation of different carbo and heterocycles with different functionalities.

Due to the known oxophilic character of Ti(III), our initial studies began testing different allyl pronucleophiles **1a-d**, and **3**, including different oxygenated functional groups such as carbonate, acetate, benzoate, methoxyl or hydroxyl groups. Moreover, an epoxyallylsilane **6** was also tested in order to compare the observed results with oxygenated functions. Remarkably, the new developments in titanocene(III)-regenerating agents now allow the use of substoichiometric amounts of Cp_2TiCl_2 as a precatalyst. In this context, the combination 2,4,6-collidine and trimethylsilyl chloride developed in our lab[30] has been extensively used and it was the choice in this case.

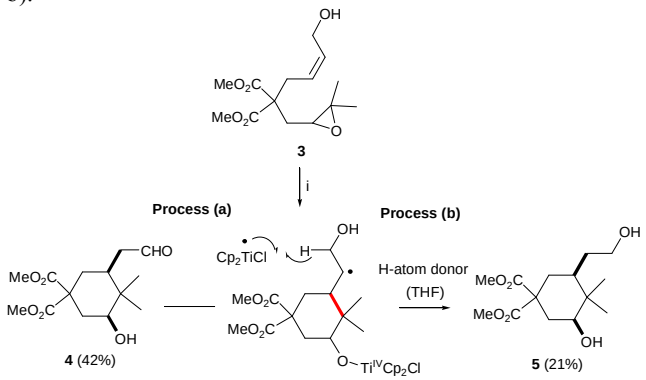
Treatment of compounds **1a-d**, with Cp_2TiCl led to the expected cyclic compound **2** with variable yields from 50-85% (Scheme 2). Noteworthy, compound **2** was obtained as a single diastereomer in all cases. NOE-diff. experiments (see experimental section) showed a *cis* relationship between hydroxyl group at C-3 and vinyl group at C-5.



Z-**1a** (R = CO_2Et), **2** (85%)
1b (R = Ac), **2** (71%)
1c (R = Bz), **2** (50%)
1d (R = Me), **2** (66%)

Scheme 2.Ti(III)-mediated cyclization of model compounds **1a-d**. Reaction conditions: i) **1a-d** (1.0 mmol) Cp_2TiCl_2 (0.2 mmol), Mn (8.0 mmol), Me_3SiCl (4.0 mmol), 2,4,6-collidine (6.0 mmol), THF, RT, 16 h. Isolated yields after column chromatography.

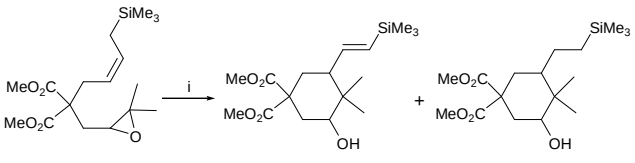
When epoxyallylic alcohol **3** was treated with Cp_2TiCl, cyclic compounds **4** and **5** were isolated in a 2/1 ratio (Scheme 3). In this case, the lack of a better leaving group resulted in a different final process. After homolytic oxirane-opening and subsequent cyclization, Ti(III)-mediated hydrogen abstraction in the radical intermediate yields aldehyde **4** (Scheme 3, process(a).[31] Besides, the radical intermediate can abstract a hydrogen-atom from the solvent (THF) leading to reduced product **5** (Scheme 3, process b).[32]



Scheme 3. Ti(III)-mediated cyclization of compound **3**. Reaction conditions: i) **3** (1.0 mmol) Cp_2TiCl_2 (0.2 mmol), Mn (8.0 mmol), Me_3SiCl (4.0 mmol), 2,4,6-collidine (6.0 mmol), THF, RT, 16 h. Isolated yields after column chromatography.

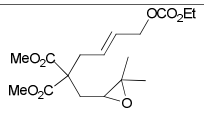
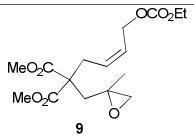
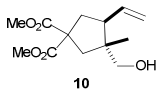
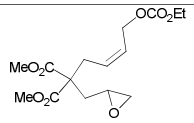
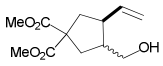
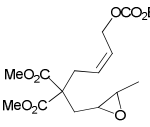
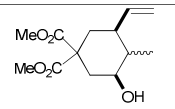
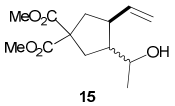
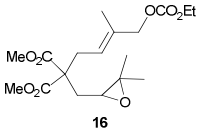
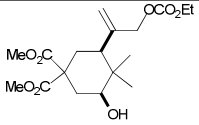
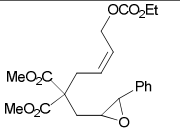
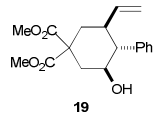
Silyl derivative **6** was assayed under the same reaction conditions, leading to a mixture of trimethylsilyl containing compounds **7** and **8** in 1/0.6 ratio (Scheme 4).[23] These two compounds were obtained by similar hydrogen-atom abstractions mentioned above. Ethyl carbonate derivative **1a** (85% yield, Scheme 2) resulted in the best yield and therefore ethyl carbonate was the leaving group of choice for the following reactions.

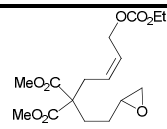
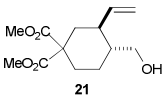
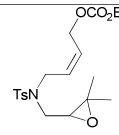
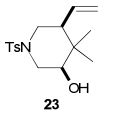
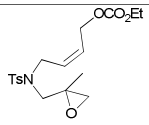
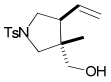
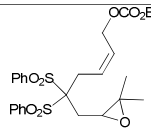
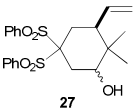
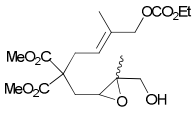
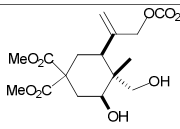
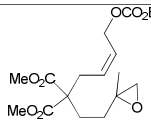
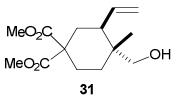
With the optimized conditions in hand, we explored substrates with different linkers, functionality and substitution patterns. The results are summarized in Table 1.



Scheme 4. Ti(III)-mediated cyclization of compound **6**. Reaction conditions: i) **6** (1.0 mmol) Cp_2TiCl_2 (0.2 mmol), Mn (8.0 mmol), Me_3SiCl (4.0 mmol), 2,4,6-collidine (6.0 mmol), THF, RT, 16 h. Isolated yield after column chromatography. Compounds **7** and **8** were not separated.

Table 1. Substrate scope of [Ti]-catalyzed intramolecular epoxide allylations

Entry	Substrate	Product	Yield (%)[a]
1	 *E*-**1a**	**2**	65%
2	 **9**	 **10**	53%
3	 **11**	 **12**	60%[b]
4	 **13**	 **14** +  **15**	55%[c]
5	 **16**	 **17**	50%[d]
6	 **18**	 **19**	54%

7	 **20**	 **21**	58%
8	 **22**	 **23**	76%
9	 **24**	 **25**	74%
10	 **26**	 **27**	71%[e]
11	 **28**	 **29**	62%[f]
12	 **30**	 **31**	73%

[a]Isolated yield after column chromatography.

[b] 7/3 Mixture of *cis*/*trans* diastereoisomers

[c] Compounds **14** and **15** were obtained in 1/1 ratio. Both compounds were obtained as diastereomeric mixture in 2/1 dr.

[d] Additional 12% of cyclic compound **S43** in which the carbonate group is eliminated was also obtained (see SI for further details)

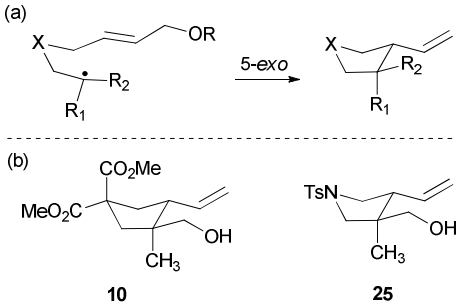
[e] 1/1 Mixture of *cis*/*trans* diastereoisomers

[f] Additional 15% of cyclic compound **S44** in which the carbonate moeity is eliminated was also obtained (see SI for further details)

The reaction successfully gave different five- and six-membered carbo-and heterocycles with excellent diastereoselectivities in almost all the tested substrates. Titanium-induced cyclization of compound *E*-**1a** (Table 1, entry 1) led to the compound **2** as *Z*-**1a** (Scheme 2), revealing the stereoconvergent nature of the process. Additionally, the reaction proved to be compatible with different functional groups, including esters (Table 1, entries 1-7 and 11-12), sulfones (Table 1, entry 10), sulphonamides (Table 1, entries 8 and 9) or free hydroxyl groups (Table 1, entry 11), and permitted different substitution patterns in the oxirane ring (Table 1, entries 1-4) as well as in the involved alkene (Table 1, entries 5 and 11).

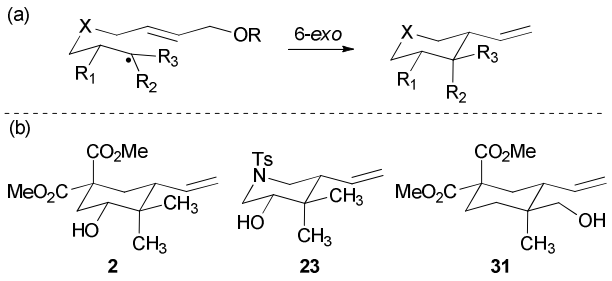
The regiochemistry of the radical epoxide opening mainly depends upon the substitution pattern[33] and controls the size of the obtained final cycle (Table 1, entries 1 *vs* 2, and entries 8 *vs* 9). As shown in entry 4, treatment of compound **13** with Cp_2TiCl led to the formation of a 1/1 mixture of five- and six-member ring, as expected from an 1,2-disubstituted oxirane ring.[8,9] However in compound **18** electronic effects control the homolytic epoxide opening thus only affording the six-membered ring **19**. Stereoconvergency was further demonstrated as diasteromeric mixture **28** (entry 11) gave rise to a single cyclic diasteromer **29**. It is also noteworthy that the stereoselectivity of this cyclization allows the setting of two stereocenters in six-membered and notably five-membered rings (entries 2 and 9). When the stereocenters are located in 1,3-relative positions a *cis* stereochemistry between hydroxyl group at C-3 and vinyl group at C-5 is observed as in the case of compounds **2**, **17** and **23** (entries 1, 5 and 8). On the other hand, compounds presenting contiguous stereocenters showed a *trans* (entries 2, 7, 9 and 12) or *cis* relationship (entry 3) between the vinyl and hydroxymethyl group depending on the substitution pattern of the intermediate radical. Interestingly, in more functionalized substrates even three stereocenters can be allocated stereoselectively (entries 6 and 11). In the case of 1,3-relative positions, *cis* stereochemistry between hydroxyl group at C-3 and vinyl group at C-5 is preserved. The additional stereocenter at C-4 presents a *trans* stereochemistry with respect to the other two stereocenters.

All these stereochemical findings can be rationalized invoking the Beckwith-Houk rules.[34,35] *Cis* substituted five-membered rings are expected for 5-exo-trig cyclizations (entry 3). Trisubstituted radicals proceed disposing the bulkier substituent (R_2 in Scheme 5a) in pseudoequatorial position (Scheme 5) thus yielding the observed cyclopentanes **10** and **25** (entries 2 and 9).



Scheme 5. (a) Ring-closure of 5-hexenyl radicals.
(b) Selected examples from Table 1.

Although cyclizations of 6-heptenyl radicals are less studied a similar reasoning explains the experimental results. In the chair-like transitions state all the bulkier substituent (R_1 and R_3 in Scheme 6) are disposed in the equatorial positions. Additional template effects cannot be ruled out in cyclization of compound **28** (entry 11).[20–23]



Scheme 6. (a) Schematic ring-closure of 6-heptenyl radicals.
(b) Selected examples from Table 2.

In the case of entries 4 and 10, the structures of compounds **13** and **26** do not follow these stereochemical trends and mixtures of

diastereoisomers are obtained. The intrinsic reactivity of a 1,2-disubstituted epoxide in compound **13** (entry 4) precludes a clear analysis of its stereoselectivity. In compound **26** (entry 10), the transition state may be affected by bulky phenyl sulphonyl groups avoiding a clear chair-like transition state and leading to formation of both isomers.

Conclusions

A useful method for the diastereoselective synthesis of vinyl substituted carbo- and heterocycles is presented. The protocol is based on the radical opening of an epoxide and subsequent intramolecular addition to an allyl carbonate. Formally, the reaction yields similar products as the allylation of epoxides by the adequate nucleophile but with several significant advantages. Firstly, the polyfunctionalized substrates required are very easily obtained and handled. Secondly, the cyclization reaction occurs at room temperature and under very smooth conditions highly compatible with diverse functional groups. And lastly, the diastereoselectivity observed is quite remarkable giving rise in most of the cases to a single diastereomer even when three stereogenic centres are generated in the final product. Highly functionalized structures difficult to achieve by other methodologies are obtained in one single step by this procedure. Thus, this method is an interesting tool in the context of organic synthesis.

Acknowledgements

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Experimental section

General Remarks. Unless otherwise stated, all reagents and solvents (CH_2Cl_2, Et_2O, MeCN, EtOAc, hexane, DMF, MeOH) were purchased from commercial sources and used without further purification. Dry THF was freshly distilled over Na/benzophenone. Flash column chromatography was carried out using Silica gel 60 (230-400 mesh, Scharlab, Spain) as the stationary phase. Analytical TLC was performed on aluminium sheets coated with silica gel with fluorescent indicator UV_{254} (Alugram SIL G/UV_{254}, Mackerey-Nagel, Germany) and observed under UV light (254 nm) and/or staining with Ce/Mo reagent or phosphomolybdic acid solution and subsequent heating. All ^1H and ^{13}C NMR spectra were recorded on Varian 300, 400 or 500 MHz spectrometers, at a constant temperature of 298 K. Chemical shifts are reported in ppm and referenced to residual solvent. Coupling constants (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: m = multiplet, quint. = quintet, q = quartet, t = triplet, d = doublet, s = singlet, b = broad. Assignment of the ^{13}C NMR multiplicities was accomplished by DEPT techniques.

Characterization data of substrates *Z*-1a, 1b-d, *E*-1a, 3, 6, 9, 11, 13, 16, 18, 20, 22, 24, 26, 28 and 30.

Compound *Z*-1a. ^1H-NMR (300 MHz, $CDCl_3$) δ(ppm): 5.75 – 5.59 (m, 1H), 5.59 – 5.43 (m, 1H), 4.64 (d, *J* = 6.7 Hz, 2H), 4.15 (q, *J* = 7.0 Hz, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 2.80 (d, *J* = 7.5 Hz, 2H), 2.70 (dd, *J* = 7.3, 4.2 Hz, 1H), 2.21 (dd, *J* = 14.8, 4.2 Hz, 1H), 1.95 (dd, *J* = 14.8, 7.3 Hz, 1H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.24 (s, 3H), 1.20 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.1 (C), 171.0 (C), 155.1 (C), 128.3 (CH), 127.2 (CH), 64.1 (CH_2), 63.2 (CH_2), 59.8 (C), 57.9 (C), 56.4 (C), 52.8 (CH_3), 52.7 (CH_3), 32.5 (CH_2), 31.6 (CH_2), 24.7 (CH_3), 18.8 (CH_3), 14.3 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{17}H_{26}O_8$ $[M+Na]^+$: 381.1519, found: 381.1525.

Compound 1b. ^1H-NMR (300 MHz, $CDCl_3$) δ(ppm): 5.70 – 5.55 (m, 1H), 5.55 – 5.40 (m, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.68 (dd, *J* = 7.3, 4.3 Hz, 1H), 2.19 (dd, *J* = 14.9, 4.3 Hz, 1H), 1.99 (s, 3H), 2.00 – 1.89 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.1 (C), 170.8 (C), 127.7 (CH), 60.1 (CH_2), 59.8 (CH), 57.9 (C), 56.3 (C), 52.8 (CH_3), 52.6 (CH_3), 32.3 (CH_2), 31.4 (CH_2), 24.6 (CH_3), 20.9 (CH_3), 18.7 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{16}H_{24}O_7Na$ $[M+Na]^+$: 351.1414, found: 351.1415.

Compound 1c. ^1H-NMR (300 MHz, $CDCl_3$) δ(ppm): 8.00 (d, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 5.87 – 5.71 (m, 1H), 5.64 – 5.50 (m, 1H), 4.86 (d, *J* = 6.7 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 2.89 (d, *J* = 7.5 Hz, 2H), 2.74 (dd, *J* = 7.4, 4.1 Hz, 1H), 2.25 (dd, *J* = 14.8, 4.1 Hz, 1H), 2.08 – 1.94 (m, 1H), 1.24 (s, 3H), 1.21 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.2 (C), 171.1 (C), 166.4 (C), 133.0 (CH), 130.2 (C), 129.6 (CH), 128.4 (CH), 128.0 (CH), 127.8 (CH), 60.6 (CH_2), 59.9 (CH), 58.0 (C), 56.4 (C), 52.8 (CH_3), 52.7 (CH_3), 32.4 (CH_2), 31.6 (CH_2), 24.7 (CH_3), 18.8 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{21}H_{26}O_7Na$ $[M+Na]^+$: 413.1570, found: 413.1569.

Compound 1d. ^1H-NMR (300 MHz, C_6D_6) δ (ppm): 5.85 – 5.68 (m, 1H), 5.60 – 5.43 (m, 1H), 3.86 (d, *J* = 6.3 Hz, 2H), 3.39 (s, 3H), 3.36 (s, 3H), 3.06 (s, 3H), 3.09 – 3.02 (m, 2H), 2.87 (dd, *J* = 8.0, 3.8 Hz, 1H), 2.45 (dd, *J* = 14.8, 3.8 Hz, 1H), 2.20 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.05 (s, 3H), 1.03 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.2 (C), 171.1 (C), 130.4 (CH), 125.9 (CH), 67.9 (CH_2), 59.8 (CH), 58.0 (CH_3), 57.9 (C), 56.3 (C), 52.7 (CH_3), 52.6 (CH_3), 32.2 (CH_2), 31.5 (CH_2), 24.6 (CH_3), 18.7 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{15}H_{24}O_6Na$ $[M+Na]^+$: 323.1465, found: 323.1474.

Compound 3. ^1H-NMR (300 MHz, C_6D_6) δ(ppm): 5.84 – 5.68 (m, 1H), 5.51 – 5.34 (m, 1H), 4.21 – 4.06 (m, 1H), 4.06 – 3.91 (m, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 3.12 (dd, *J* = 14.8, 8.5 Hz, 1H), 2.98 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.80 (dd, *J* = 8.3, 3.2 Hz, 1H), 2.48 (dd, *J* = 14.9, 3.2 Hz, 1H), 2.12 (dd, *J* = 14.9, 8.3 Hz, 1H), 1.00 (s, 3H), 0.99 (s, 3H).^{13}C-NMR (75 MHz, C_6D_6) δ(ppm): 171.5 (C), 171.3 (C), 134.0 (CH), 125.0 (CH), 60.1 (CH), 58.1 (CH_2), 57.7 (C), 57.1 (C), 52.4 (CH_3), 52.3 (CH_3), 32.8 (CH_2), 31.6 (CH_2), 24.5 (CH_3), 18.6 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{22}O_6Na$ $[M+Na]^+$: 309.1308, found: 309.1307.

Compound 6. ^1H-NMR (300 MHz, $CDCl_3$) δ(ppm): 5.62 – 5.45 (m, 1H), 5.18 – 5.01 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 2.80 – 2.72 (m, 1H), 2.71 (d, *J* = 7.0 Hz, 2H), 2.20 (dd, *J* = 14.8, 4.6 Hz, 1H), 2.00 (dd, *J* = 14.8, 7.3 Hz, 1H), 1.42 (d, *J* = 8.0 Hz, 2H),

1.28 (s, 3H), 1.24 (s, 3H), -0.02 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.6 (C), 132.0 (CH), 121.3 (CH), 60.1 (CH_2), 58.0 (C), 56.8 (C), 52.6 (CH_3), 52.5 (CH_3), 36.9 (CH_2), 32.0 (CH_2), 24.8 (CH_3), 23.1 (CH_3), 18.8 (CH_3), -1.9 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{17}H_{31}O_5Si$ $[M+H]^+$: 343.1941, found: 343.1951.

Compound *E*-1a. ^{1}H-NMR (300 MHz, acetone) δ(ppm): 5.75 – 5.65 (m, 2H), 4.69 (d, *J* = 6.4 Hz, 2H, *Z*-isomer), 4.54 (d, *J* = 6.4 Hz, 2H, *E*-isomer), 4.19 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 2.84 (d, *J* = 7.2 Hz, 2H, *Z*-isomer), 2.81 – 2.69 (m, 3H), 2.22 (dd, *J* = 14.9, 4.2 Hz, 1H), 1.99 (dd, *J* = 14.9, 7.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.28 (s, 3H), 1.25 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.0 (C), 170.9 (C), 154.8 (C), 129.7 (CH), 128.4 (CH), 67.5 (CH_2), 63.9 (CH_2), 59.7 (CH), 57.8 (C), 56.5 (CH), 52.6 (CH_3), 52.5 (CH_3), 36.2 (CH_2), 32.2 (CH_2), 24.6 (CH_3), 18.7 (CH_3), 14.2 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{17}H_{26}O_8Na$ $[M+Na]^+$: 381.1519, found: 381.1516.

Compound 9. ^{1}H-NMR (300 MHz, C_6D_6) δ(ppm): 5.74 – 5.46 (m, 2H), 4.63 (d, *J* = 5.7 Hz, 2H), 3.91 (q, *J* = 7.1 Hz, 2H), 3.35 (s, 6H), 3.00 – 2.89 (m, 2H), 2.31 (d, *J* = 3.9 Hz, 2H), 2.26 (d, *J* = 5.1 Hz, 1H), 2.11 (d, *J* = 5.1 Hz, 1H), 1.10 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, C_6D_6) δ(ppm): 171.2 (C), 171.0 (C), 155.5 (C), 128.9 (CH), 127.4 (CH), 63.7 (CH_2), 63.1 (CH_2), 56.7 (C), 54.0 (CH_2), 53.9 (C), 52.2 (CH_3), 52.2 (CH_3), 39.9 (CH_2), 32.1 (CH_2), 21.6 (CH_3), 14.2 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{16}H_{24}O_8Na$ $[M+Na]^+$: 367.1363, found: 367.1372.

Compound 11. ^{1}H-NMR (300 MHz, C_6D_6) δ(ppm): 5.69 – 5.54 (m, 1H), 5.56 – 5.38 (m, 1H), 4.61 (d, *J* = 6.7 Hz, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.35 (s, 3H), 3.33 (s, 3H), 2.93 (d, *J* = 7.8 Hz, 2H), 2.87 – 2.76 (m, 1H), 2.33 – 2.20 (m, 2H), 1.98 (dd, *J* = 5.2, 2.4 Hz, 1H), 1.88 (dd, *J* = 14.7, 7.8 Hz, 1H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, C_6D_6) δ(ppm): 171.0 (C), 170.9 (C), 155.5 (C), 128.5 (CH), 127.8 (CH), 63.8 (CH_2), 63.1 (CH_2), 56.7 (CH_2), 52.3 (CH_3), 48.2 (CH), 46.0 (CH_2), 36.8 (CH_2), 31.9 (CH_2), 14.2 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{15}H_{22}O_8Na$ $[M+Na]^+$: 353.1206, found: 353.1197.

Compound 13. 5.69 – 5.56 (m, 1H), 5.56 – 5.41 (m, 1H), 4.61 (d, *J* = 6.9 Hz, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 3.34 (s, 3H), 2.94 (d, *J* = 7.8 Hz, 2H), 2.76 – 2.68 (m, 1H), 2.44 – 2.34 (m, 1H), 2.28 (dd, *J* = 14.6, 4.2 Hz, 1H), 2.02 (dd, *J* = 14.6, 7.4 Hz, 1H), 0.96 (d, *J* = 5.2 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H).^{13}C-NMR (75 MHz, C_6D_6) δ(ppm): 170.9 (C), 155.0 (C), 128.2 (CH), 127.2 (CH), 64.0 (CH_2), 63.1 (CH_2), 56.2 (C), 55.4 (CH), 54.3 (CH), 52.8 (CH_3), 52.7 (CH_3), 35.9 (CH_2), 31.6 (CH_2), 17.3 (CH_3), 14.3 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{16}H_{24}O_8$ $[M+Na]^+$: 367.1363, found: 367.1377.

Compound 16. ^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 5.56 (t, *J* = 7.0 Hz, 1H), 4.40 (s, 2H), 3.93 (q, *J* = 7.1 Hz, 2H), 3.38 (s, 3H), 3.36 (s, 3H), 3.00 (t, *J* = 7.0 Hz, 2H), 2.86 (dd, *J* = 7.9, 4.1 Hz, 1H), 2.43 (dd, *J* = 14.8, 4.1 Hz, 1H), 2.20 (dd, *J* = 14.8, 7.9 Hz, 1H), 1.51 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.4 (C), 171.2, (C) 155.4 (C), 134.4 (C), 122.9 (CH), 72.6 (CH_2), 63.7 (CH_2), 59.7 (CH), 57.3 (C), 56.8 (C), 52.3 (CH_3), 52.2 (CH_3), 32.9 (CH_2), 32.1 (CH_2), 24.6 (CH_3), 18.7 (CH_3), 14.2 (CH_3), 13.9 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{18}H_{28}O_8Na$ $[M+Na]^+$: 395.1676, found: 395.1667.

Compound 18. ^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 7.36 – 7.25 (m, 3H), 7.26 – 7.16 (m, 2H), 5.78 – 5.61 (m, 2H), 4.52 (d, *J* = 4.5 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 3.56 (d, J = 1.8 Hz, 1H), 2.96 (ddd, J = 6.7. 5.0. 1.8 Hz, 1H), 2.77 (d, *J* = 5.7 Hz, 2H), 2.27 (dd, *J* = 14.7, 5.0 Hz, 1H), 2.14 (dd, *J* = 14.7, 6.7 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 170.9 (C), 154.9 (C), 136.9 (C), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 125.6 (CH), 67.5 (CH_2), 64.0 (CH_2), 58.8 (CH), 58.5 (CH), 56.4 (C), 52.8 (CH_3), 36.7 (CH_2), 36.2 (CH_2), 14.3 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{21}H_{26}O_8Na$ $[M+Na]^+$: 429.1519, found: 429.1529.

Compound 20. ^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 5.76 – 5.59 (m, 2H), 4.54 (d, *J* = 4.5 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 6H), 2.95 – 2.85 (m, 1H), 2.79 – 2.70 (m, 1H), 2.65 (d, *J* = 5.5 Hz, 2H), 2.51 – 2.42 (m, 1H), 2.11 – 1.91 (m, 2H), 1.54 – 1.38 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.1 (C), 154.9 (C), 129.7 (CH), 128.1 (CH), 67.5 (CH_2), 63.9 (CH_2), 57.1 (C), 52.5 (CH_3), 51.7 (CH), 46.9 (CH_2), 35.9 (CH_2), 28.9 (CH_2), 27.3 (CH_2), 14.2 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{16}H_{24}O_8Na$ $[M+Na]^+$: 367.1363, found: 367.1362.

Compound 22. ^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 7.71 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.79 – 5.64 (m, 1H), 5.64 – 5.51 (m, 1H), 4.68 (d, *J* = 6.7 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.09 – 3.90 (m, 2H), 3.65 (dd, *J* = 14.8, 3.7 Hz, 1H), 2.95 (dd, *J* = 14.8, 5.7 Hz, 1H), 2.87 (dd, *J* = 5.7, 3.7 Hz, 1H), 2.43 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.28 (s, 3H), 1.24 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 154.9 (C), 143.6 (C), 136.6 (C), 129.8 (CH), 129.6 (CH), 127.2 (CH), 127.1 (CH), 64.1 (CH_2), 62.7 (CH_2), 61.9 (CH), 57.8 (C), 47.1 (CH_2), 45.3 (CH_2), 24.4 (CH_3), 21.5 (CH_3), 18.8 (CH_3), 14.2 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{19}H_{28}NO_6S$ $[M+H]^+$: 398.1637, found: 398.1627.

Compound 24. ^{1}H-NMR (300 MHz, C_6D_6) δ(ppm): 7.65 (d, *J* = 8.2 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 5.55 – 5.34 (m, 2H), 4.63 (d, *J* = 6.2 Hz, 2H), 3.91 (d, *J* = 6.1 Hz, 2H), 3.88 (q, *J* = 7.1 Hz, 2H), 3.35 (d, *J* = 14.5 Hz, 1H), 2.79 (d, *J* = 14.5 Hz, 1H), 2.25 (d, *J* = 4.8 Hz, 1H), 2.10 (d, *J* = 4.8 Hz, 1H), 1.90 (s, 3H), 1.20 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H).^{13}C-NMR (75 MHz, acetone) δ(ppm): 155.7 (C), 144.4 (C), 138.2 (C), 130.7 (CH), 130.1 (CH), 128.1 (CH), 127.9 (CH), 64.4 (CH_2), 63.5 (CH_2), 56.2 (CH_2), 53.6 (CH), 51.9 (CH_2), 46.3 (CH_2), 21.5 (CH_3), 19.2 (CH_3), 14.6 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{18}H_{26}NO_6S$ $[M+H]^+$: 384.1481, found: 384.1476.

Compound 26. ^{1}H-NMR (300 MHz, C_6D_6) δ(ppm): 8.22 – 8.11 (m, 4H), 7.09 – 6.93 (m, 6H), 6.08 (dt, *J* = 11.0, 6.5 Hz, 1H), 5.55 (dt, *J* = 11.0, 6.6 Hz, 1H), 4.43 (d, *J* = 6.8 Hz, 2H), 3.88 (q, *J* = 7.1 Hz, 2H), 3.49 (t, *J* = 4.9 Hz, 1H), 3.36 (d, *J* = 6.5 Hz, 2H), 2.81 (dd, *J* = 16.1, 4.9 Hz, 1H), 2.50 (dd, *J* = 16.1, 4.9 Hz, 1H), 1.16 (s, 3H), 1.02 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).^{13}C-NMR (75 MHz, C_6D_6) δ(ppm): 155.4 (C), 137.4 (C), 137.2 (C), 134.6 (CH), 134.5 (CH), 132.0 (CH), 131.9 (CH), 128.8 (CH), 128.7 (CH), 127.6 (CH), 126.8 (CH), 89.8 (C), 63.9 (CH_2), 62.8 (CH_2), 58.7 (CH), 58.5 (C), 30.6 (CH_2), 28.9 (CH_2), 24.5 (CH_3), 18.8 (CH_3), 14.2 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{25}H_{30}O_8S_2Na$ $[M+Na]^+$: 545.1274, found: 545.1260.

Compound 28. ^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 5.31 (t, *J* = 7.3 Hz, 1H), 4.42 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 3.57 (s, 2H), 2.80 (dd, *J* = 6.9, 5.2 Hz, 1H), 2.71 (d,

J = 7.3 Hz, 2H), 2.19 (dd, J = 14.9, 5.2 Hz, 1H), 2.03 (dd, J = 14.9, 6.9 Hz, 1H), 1.63 (s, 3H), 1.30 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.3 (C), 171.2 (C), 155.0 (C), 134.1 (C), 122.6 (CH), 72.7 (CH_2), 64.0 (CH_2), 63.5 (CH_2), 60.6 (CH), 60.4 (C), 56.3 (C), 52.8 (CH_3), 52.7 (CH_3), 32.0 (CH_2), 31.6 (CH_2), 19.9 (CH_3), 14.2 (CH_3), 14.0 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{18}H_{28}O_9Na$ $[M+Na]^+$: 411.1625, found: 411.1624.

Compound 30. ^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 5.72 – 5.59 (m, 1H), 5.53 – 5.40 (m, 1H), 4.61 (d, J = 6.8 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.67 (s, 6H), 2.65 (d, J = 7.6 Hz, 2H), 2.53 (dd, J = 11.9, 4.7 Hz, 2H), 1.92 (t, J = 8.3 Hz, 2H), 1.51 – 1.31 (m, 2H), 1.26 (t, J = 7.1Hz, 3H), 1.25 (s, 3H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.2 (C), 155.0 (C), 128.3 (CH), 127.0 (CH), 64.0 (CH_2), 63.0 (CH_2), 57.0 (C), 56.4 (C), 53.5 (CH_2), 52.6 (CH_3), 31.3 (CH_2), 30.8 (CH_2), 28.2 (CH_2), 20.8 (CH_3), 14.3 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{17}H_{27}O_8$ $[M+H]^+$: 359.1706, found: 359.1719.

General procedure for the intramolecular epoxide allylation. Rigorously deoxygenated dry THF (10 mL) was added to a previously deoxygenated mixture of Cp_2TiCl_2 (0.2 mmol), Mn (8.0 mmol) under Ar atmosphere, and the suspension was stirred at room temperature until it turned green (about 10 min). A solution of the previously synthesized polyfunctionalized substrate (1.0 mmol) in THF (2 mL), Me_3SiCl (4.0 mmol) and 2,4,6-collidine (6.0 mmol) were then added. The reaction mixture was stirred at room temperature for 16 h and then diluted with EtOAc, washed with HCl (10%), dried over anhydrous Na_2SO_4 and the solvent removed. The residue was submitted to flash column chromatography (SiO_2, EtOAc:Hexane mixtures) to give the corresponding cyclic products.

Characterization data of cyclic products 2, 4, 5, 7, 8, 10, 12, 14, 15, 17, 19, 21, 23, 25, 27, 29, and 31. (See SI for numbering and copies of ^{1}H-NMR and ^{13}C-NMR spectra).

Compound 2. Colorless oil; 65 - 85% yield.^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 5.69 (ddd, J = 17.2, 10.4, 8.1 Hz, 1H), 5.06 (dd, J = 10.4, 1.8 Hz, 1H), 5.03 (d, J = 17.2 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.40 (dd, J = 12.1, 4.2 Hz, 1H), 2.37 (ddd, J = 12.1, 4.2, 2.4 Hz, 1H), 2.10 (dt, J = 13.6, 2.7 Hz, 1H), 1.90 (ddd, J = 12.7, 8.1, 2.7 Hz, 1H), 1.82 (t, J = 12.7 Hz, 1H), 1,80 (t, J = 13.2 Hz, 1H), 0.95 (s, 3H), 0.77 (s, 3H); NOE-diff. experiment: proton irradiated, (NOEs observed): H-7, (H_2-8, H-5); H-3, (H-2b H-5).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 171.9 (C), 171.5 (C), 137.7 (CH), 116.6 (CH_2), 74.4 (CH), 54.9 (C), 52.9 (CH_3), 52.8 (CH_3), 47.0 (CH), 38.0 (C), 34.7 (CH_2), 31.9 (CH_2), 25.6 (CH_3), 12.3 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{22}O_5Na$ $[M+Na]^+$: 293.1359, found: 293.1351.

Compound 4. Colorless oil; 40% yield.^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 9.74 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.46 (dd, J = 11.9, 3.8 Hz, 1H), 2.57 (dd, J = 16.8, 2.4 Hz, 1H), 2.39 (ddd, J = 13.2, 4.0, 2.3 Hz, 1H), 2.17 (dd, J = 10.0, 2.9 Hz, 1H), 2.12 (dt, J = 13.2, 3.5 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.80 (t, J = 12.6 Hz, 1H), 1.61 (t, J = 13.4 Hz, 1H), 0.99 (s, 3H), 0.77 (s, 3H); NOE-diff. experiment: proton irradiated, (NOEs observed): H-7a, (H-7b, H-5); H-3 (H-2a, H-5), H-2a (H-2b, H-3).^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 201.8 (C), 171.5 (C), 171.2 (C), 73.9 (CH), 54.7 (C), 53.0 (CH_2), 52.9 (CH_2), 44.6 (CH_2), 38.0 (C), 36.5 (CH), 34.7 (CH_2), 32.5 (CH_2), 25.1 (CH_3), 12.4 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{22}O_6Na$ $[M+Na]^+$: 309.1308, found: 309.1308.

Compound 5. Colorless oil; 23% yield.^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 3.75 (s, 3H), 3.71 (s, 3H), 3.71 - 3.57 (m, 2H), 3.34 (dd, J = 11.8, 4.0 Hz, 1H), 2.39 (ddd, J = 13.2, 3.9, 2.3 Hz, 1H), 2.25 (dt, J = 13.8, 2.7 Hz, 1H), 1.86 (t, J = 12.0 Hz, 1H), 1.85 - 1.77 (m, 1H), 1.63 - 1.57 (bs, 2H), 1.51 (t, J = 13.0 Hz, 1H), 1.38 – 1.17 (m, 2H), 1.00 (s, 3H), 0.77 (s, 3H).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 171.9 (C), 171.5 (C), 74.6 (CH), 61.5 (CH_2), 54.9 (C), 53.0 (CH_2), 52.9 (CH_2), 38.6 (CH), 38.3 (C), 34.7 (CH_2), 32.2 (CH_2), 31.7 (CH_2), 24.9 (CH_3), 12.2 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{24}O_6Na$ $[M+Na]^+$: 311.1465, found: 311.1468.

Compound 7 and 8. Compounds **7** and **8** were isolated as a mixture in a **7**/**8** ratio of 1.6/1. Colorless oil; 53% yield. (Compounds **7** (33% yield) and **8** (20% yield) were not separated).^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 5.89 (dd, J = 18.7, 7.0 Hz, 1H, **7**), 5.67 (d, J = 18.7 Hz, 1H, **7**), 3.75 (s, 3H, **7**), 3.74 (s, 3H, **8**), 3.71 (s, 3H), 3.40 (dd, J = 12.0, 4.1 Hz, 1H, **7**), 3.34 (dd, J = 12.0, 4.0 Hz, 1H, **8**), 2.37 (ddd, J = 12.6, 4.0, 2.2 Hz, 1H), 2.11 (dt, J = 12.8, 2.0 Hz, 1H), 1.96 □ 1.74 (m, 3H), 1.60 □ 1.50 (m, 1H, **8**), 1.40 (t, J = 13.0 Hz, 1H, **8**), 0.99 (s, 3H, **8**), 0.95 (s, 3H, **7**), 0.94 – 0.80 (m, 2H, **8**) 0.77 (s, 3H, **7**), 0.73 (s, 3H, **8**), 0.72 – 0.61 (m, 1H, **8**), 0.35 – 0.20 (m, 1H, **8**), 0.04 (s, 9H, **7**), 0.03 (s, 9H, **8**).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 172.2 (C), 171.9 (C), 171.6 (C), 171.5 (C), 145.2 (CH, **7**), 132.6 (CH, **7**), 74.6 (CH), 74.4 (CH), 54.9 (C), 54.8 (C), 53.0 (CH_3), 52.9 (CH_3), 52.8 (CH_3), 52.7 (CH_3), 49.1 (CH), 45.7 (CH), 38.7 (C), 38.1 (C), 34.8 (CH_2), 34.6 (CH_2), 31.7 (CH_2), 31.2 (CH_2), 25.6 (CH_3), 25.0 (CH_3), 23.2 (CH_2, **8**), 15.1 (CH_2, **8**), 12.4 (CH_3), 12.1 (CH_3), -1.6 (CH_3), -1.1 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{17}H_{30}O_5Si$ $[M]^+$: 342.1863, found: 342.1867. HRMS for compound **8** was not found.

Compound 10. Colorless oil; 53% yield.^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 5.74 – 5.62 (m, 1H), 5.06 (d, J = 16.1 Hz, 1H), 5.05 (d, J = 11.3 Hz, 1H), 3.71 (s, 6H), 3.41 (d, J = 10.9 Hz, 1H), 3.36 (d, J = 10.9 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.43 (d, J = 14.2 Hz, 1H), 2.42 □ 2.37 (m, 1H), 2.28 (t, J = 12.8 Hz, 1H), 2.06 (d, J = 14.2 Hz, 1H), 0.82 (s, 3H); NOE-diff. experiment: proton irradiated, (NOEs observed): H_3-8, (H-2b, H_2-9, H-6), H-6, (H_2-5, H-4, H_3-8), H-4, (H-6, H_2-7, H_2-5, H_2-9). ^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 173.5 (C), 172.9 (C), 137.3 (CH), 116.7 (CH_2), 69.3 (CH_2), 57.9 (C), 53.1 (CH_3), 52.9 (CH_3), 48.1 (CH), 46.9 (C), 43.5 (CH_2), 38.5 (CH_2), 19.3 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 279.1202, found: 279.1200.

Compound 12. Compound **12** was obtained as a 7/3 mixture of *cis/trans* diastereoisomers. Colorless oil; 60% yield.^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 5.85 (ddd, J = 17.3, 10.2, 8.5 Hz, 1H, *cis*-**12**), 5.70 (ddd, J = 17.4, 10.1, 8.1 Hz, 1H, *trans*-**12**), 5.09 (d, J = 16.6 Hz, 1H, *cis*-**12**), 5.05 (d, J = 8.6 Hz, 1H, *cis*-**12**), 5.07 □ 4.95 (m, 2H, *trans*-**12**), 3.72 (bs, 6H), 3.68 □ 3.52 (m, 2H, *trans*-**12**), 3.61 (dd, J = 11.1, 6.4 Hz, 1H, *cis*-**12**), 3.48 (dd, J = 11.1, 6.3 Hz, 1H, *cis*-**12**), 2.88 □ 2.74 (m, 1H), 2.54 □ 2.23 (m, 3H), 2.19-1.98 (m, 2H).^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 173.1 (C), 173.0 (C), 172.9 (C), 172.0 (C), 140.3 (CH), 137.8 (CH), 116.1 (CH_2), 115.9 (CH_2), 64.4 (CH_2), 63.2 (CH_2), 59.2 (C), 58.8 (C), 53.0 (CH_3), 52.9 (CH_3), 47.3 (CH), 46.5 (CH), 45.1 (C), 44.9 (CH), 40.9 (CH_2), 39.1 (CH_2), 37.1 (CH_2), 36.5

(CH_2). HRMS (TOF MS ES+) *m/z* calcd. for $C_{12}H_{18}O_5Na$ $[M+Na]^+$: 265.1046, found: 265.1054. Compound **12** was oxidized to simplify the ^{1}H-NMR spectrum and confirm the ratio of diastereomers obtained. See SI for further details.

Compound 14 and 15. Compounds **14** and **15** were both obtained as a mixture of diastereoisomers. Yellowish oil; 55% yield. Compounds **14** and **15** were not separated.^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 5.90 - 5.73 (m, 1H, **14** or **15**), 5.63 - 5.48 (m, 1H, **14** or **15**), 5.10 - 4.96 (m, 2H), 3.82 - 3.72 (m, 1H, **14** or **15**), 3.73 (bs, 3H, **14** or **15**), 3.71 (bs, 3H), 3.69 (bs, 3H, **14** or **15**), 3.37 - 3.26 (m, 1H, **14** or **15**), 2.61 - 2.39 (m, 2H), 2.35 - 2.14 (m, 2H), 2.08 - 1.96 (m, 1H), 1.93 - 1.72 (m, 1H), 1.69 - 1.54 (m, 1H), 1.15 (d, *J* = 4.3 Hz, 3H, **15**), 0.96 (d, *J* = 6.0 Hz, 3H, **14**). HRMS (TOF MS ES+) *m/z* calcd. for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 279.1202, found: 279.1210. The mixture of compounds **14** and **15** was oxidized to simplify the ^{1}H-NMR spectrum and confirm both compounds and dr obtained. See SI for further details.

Compound 17. Colorless oil; 50% yield.^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 5.29 (s, 1H), 5.02 (s, 1H), 4.54 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 3.42 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.39 (ddd, *J* = 13.2, 4.0, 2.3 Hz, 1H), 2.14 (dt, *J* = 13.7, 2.6 Hz, 1H), 2.00 (t, *J* = 14.2 Hz, 1H), 1.91 – 1.85 (m, 1H), 1.84 (t, *J* = 14.2 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.95 (s, 3H), 0.87 (s, 3H); NOE-diff. experiment: proton irradiated, (NOEs observed): H-3, (H-2a, H-5). ^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 171.7 (C), 171.3 (C), 155.1 (C), 143.5 (C), 115.3 (CH_2), 74.7 (CH), 71.1 (CH_2), 64.2 (CH_2), 54.9 (C), 53.0 (CH_3), 52.8 (CH_3), 44.6 (CH), 39.1 (C), 34.6 (CH_2), 32.5 (CH_2), 25.7 (CH_3), 14.4 (CH_3), 12.7 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{18}H_{28}O_8Na$ $[M+Na]^+$: 395.1676, found: 395.1668.

Compound 19. Colorless oil; 54% yield.^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 7.31 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.20 (m, 1H), 7.14 (dd, *J* = 8.3, 1.4 Hz, 2H), 5.43 (ddd, *J* = 17.5, 10.4, 7.1 Hz, 1H), 4.83 (d, *J* = 16.1 Hz, 1H), 4.81 (d, *J* = 9.4 Hz, 1H), 3.86 (td, *J* = 11.2, 4.7 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.74 (ddd, *J* = 13.1, 4.7, 2.2 Hz, 1H), 2.55 – 2.44 (m, 2H), 2.27 (dd, *J* = 11.2, 10.6 Hz, 1H), 1.82 (dd, *J* = 13.1, 11.2 Hz, 1H), 1.74 (dd, *J* = 13.4, 12.2 Hz, 1H). NOE-diff. experiment: proton irradiated, (NOEs observed): H-7, (H_2-8, H-4, H-6b), H-4, (H-2b, H-6b), H-3, (H_2-2, H-5).^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 171.8 (C), 171.4 (C), 140.1 (C), 139.6 (CH), 128.8 (CH), 127.3 (CH), 115.5 (CH_2), 71.2 (CH), 57.4 (CH), 54.8 (C), 53.1 (CH_3), 52.9 (CH_3), 42.3 (CH), 38.1 (CH_2), 36.6 (CH_2). HRMS (TOF MS ES+) *m/z* calcd. for $C_{18}H_{22}O_5Na$ $[M+Na]^+$: 341.1359, found: 341.1359.

Compound 21. Colorless oil; 58% yield.^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 5.64 (ddd, *J* = 17.2, 10.1, 9.0 Hz, 1H), 5.10 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.03 (dd, *J* = 10.1, 1.5 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.62 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.40 (dd, *J* = 11.0, 6.1 Hz, 1H), 2.41 (ddd, *J* = 13.5, 6.0, 3.2 Hz, 1H), 2.35 – 2.27 (m, 1H), 2.10 – 1.96 (m, 1H), 1.84 (ddd, *J* = 13.6, 7.1, 3.9 Hz, 1H), 1.71 (td, *J* = 13.6, 3.9 Hz, 1H), 1.63 – 1.53 (m, 1H), 1.39 – 1.14 (m, 2H). 2D- NOESY spectra observed: H-5 (H-9); H-5 (H-6); H-5 (H-3a); H-4 (H_2-11); H-4 (H-3b). ^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 172.69 (C), 171.52 (C), 141.76 (CH), 115.87 (CH_2), 66.33 (CH_2), 54.90 (C), 52.85 (CH_3), 52.67 (CH_3), 43.34 (CH), 41.80 (CH), 37.44 (CH_2), 30.73 (CH_2), 25.59 (CH_2). HRMS (TOF MS ES+) *m/z* calcd. for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 279.1201, found: 279.1215.

Compound 23. White solid; M. p. 121 □ 123 ºC. 76% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 7.65 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 5.58 (ddd, *J* = 17.1, 10.4, 8.6 Hz, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 5.09 (d, *J* = 17.1 Hz, 1H), 3.65 (ddd, *J* = 11.2, 4.8, 1.7 Hz, 1H), 3.54 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.46 (ddd, *J* = 11.8, 4.2, 1.7 Hz, 1H), 2.44 (s, 3H), 2.35 (dd, *J* = 23.9, 11.4 Hz, 2H), 2.21 – 2.14 (m, 1H), 0.97 (s, 3H), 0.65 (s, 3H). NOE-diff. experiment: proton irradiated, (NOEs observed): H-5, (H-6, H-3), H-3, (H-2, H-5).^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 143.7 (C), 134.3 (CH), 129.8 (CH), 127.7 (CH), 118.7 (CH_2), 74.2 (CH), 49.2 (CH), 47.4 (CH_2), 46.0 (CH_2), 37.1 (C), 25.2 (CH_3), 21.7 (CH_3), 12.3 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{16}H_{24}NO_3S$ $[M+H]^+$: 310.1471, found: 310.1481.

Compound 25. Colorless oil; 74% yield.^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 7.70 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.51 (ddd, *J* = 17.1, 10.3, 8.5 Hz, 1H), 5.06 (d, *J* = 10.3 Hz, 1H), 5.00 (d, *J* = 17.1 Hz, 1H),3.49 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.34 (dd, *J* = 17.9, 10.9 Hz, 2H), 3.29 (d, *J* = 9.8 Hz, 1H), 3.13 (t, *J* = 9.9 Hz, 1H), 3.06 (d, *J* = 9.8 Hz, 1H), 2.57 (dd, *J* = 17.1, 8.0 Hz, 1H), 2.42 (s, 3H), 0.71 (s, 3H). NOE-diff. experiment: proton irradiated, (NOEs observed): H-6, (H-5, H_2-9, H_3-8), H-4, (H-6, H_2-7, H-5, H_2-9), H_3-8, (H-2, H_2-9, H-6).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 143.6 (C), 134.3 (CH), 129.7 (CH), 127.5 (CH), 118.4 (CH_2), 67.0 (CH_2), 56.6 (CH_2), 51.0 (CH_2), 47.1 (CH), 46.4 (C), 21.6 (CH_3), 16.9 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{15}H_{22}NO_3S$ $[M+H]^+$: 296.1314, found: 296.1326.

Compound *trans*-27. Vitreous solid; 39% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 8.14 (dd, *J* = 8.5, 1.2 Hz, 2H), 8.02 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.74 (dd, *J* = 15.3, 7.2 Hz, 2H), 7.63 (dd, *J* = 15.3, 7.2 Hz, 4H), 5.70 (ddd, *J* = 17.2, 10.9, 8.3 Hz, 1H), 5.14 (d, *J* = 10.9 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 4.27 (d, *J* = 11.4 Hz, OH), 3.60 (ddd, *J* = 11.4, 4.9, 2.0 Hz, 1H), 2.92 (dd, *J* = 16.5, 4.9 Hz, 1H), 2.81 (ddd, *J* = 12.4, 8.3, 3.8 Hz, 1H), 2.52 (d, *J* = 18.6 Hz, 1H), 2.49 (t, *J* = 13.0 Hz, 1H), 2.18 (ddd, *J* = 15.7, 3.8, 1.7 Hz, 1H), 1.04 (s, 3H), 0.82 (s, 3H). NOE-diff. experiment: proton irradiated, (NOEs observed): H-5, (H-7, H-6), H-3, (H-2, H-6). ^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 137.47 (CH), 135.78 (C), 135.04 (CH), 134.94 (C), 134.84 (CH), 132.04 (CH), 131.75 (CH), 128.83 (CH), 128.79 (CH), 117.67 (CH_2), 89.02 (C), 74.24 (CH), 40.32 (CH), 36.98 (C), 28.59 (CH_2), 27.34 (CH_2), 25.57 (CH_3), 19.34 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{22}H_{26}O_5S_2Na$ $[M+Na]^+$: 457.1113, found: 457.1100

Compound *cis*-27. White solid; M. p. 153 – 156 ºC. 32% yield.^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.07 (d, *J* = 7.6 Hz, 2H), 8.02 (d, *J* = 7.6 Hz, 2H), 7.76 – 7.67 (m, 2H), 7.65 – 7.56 (m, 4H), 5.64 (ddd, *J* = 17.3, 10.8, 8.8 Hz, 1H), 5.11 (d, *J* = 10.8 Hz, 1H), 5.10 (d, *J* = 17.3 Hz, 1H), 4.24 – 4.09 (m, 1H), 2.68 (ddd, *J* = 12.5, 8.8, 3.8 Hz, 1H), 2.52 – 2.24 (m, 3H), 2.06 – 1.95 (m, 1H), 1.02 (s, 3H), 0.71 (s, 3H). NOE-diff. experiment: proton irradiated, (NOEs observed): H-5, (H-7, H-3, H-6), H-3, (H-5, H-2).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 137.0 (CH), 135.9 (C), 134.8 (CH), 134.6 (CH), 131.7 (CH), 131.3 (CH), 128.7 (CH), 117.7 (CH_2), 88.6 (C), 73.0 (CH), 45.8 (CH), 37.6 (C), 30.4 (CH_2), 27.0 (CH_2), 25.3 (CH_3), 11.7 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{22}H_{26}O_5S_2Na$ $[M+Na]^+$: 457.1113, found: 457.1092.

Compound 29. Colorless oil; 62% yield.^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 5.30 (s, 1H), 5.07 (s, 1H), 4.54 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.87 (dd, *J* = 12.2, 4.2 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.60 (d, *J* = 10.8 Hz, 1H), 3.38 (d, *J* = 10.8 Hz, 1H), 2.42 (ddd, *J* = 13.2, 4.1, 2.2 Hz, 1H), 2.19 (dt, *J* = 13.5, 2.7 Hz, 1H), 2.16 – 2.12 (m, 1H), 2.01 (t, *J* = 13.1 Hz, 1H), 1.95 (t, *J* = 12.5 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 3H). 2D- NOESY spectra observed: H-3 (H-2a); H-3 (H-5); H-3 (H-11); H-5 (H-11).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 171.6 (C), 171.2 (C), 155.2 (C), 143.3 (C), 116.1 (CH_2), 71.2 (CH), 71.1 (CH_2), 68.3 (CH_2), 64.4 (CH_2), 54.7 (C), 53.1 (CH_3), 52.9 (CH_3), 43.1 (C), 39.0 (CH), 34.2 (CH_2), 32.4 (CH_2), 14.4 (CH_3), 9.3 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{18}H_{28}O_9Na$ $[M+Na]^+$: 411.1625, found: 411.1627.

Compound 31. Yellowish oil; 73% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 5.69 (ddd, *J* = 17.2, 10.2, 8.8 Hz, 1H), 5.09 (d, *J* = 17.2 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.34 (d, *J* = 11.0 Hz, 1H), 3.29 (d, *J* = 11.0 Hz, 1H), 2.30 – 2.20 (m, 2H), 2.15 (ddd, *J* = 11.0, 3.5, 2.4 Hz, 1H), 1.89 (td, *J* = 13.7, 3.5 Hz, 1H), 1.82 (t, *J* = 13.0 Hz, 1H), 1.50 (td, *J* = 13.9, 3.7 Hz, 1H), 1.35 (dt, *J* = 13.9, 3.6 Hz, 1H), 0.84 (s, 3H). NOE-diff. experiment: proton irradiated, (NOEs observed): H-7, (H-8, H_3-9), H_2-10, (H-5, H_3-9), H_3-9, (H-7, H_2-10).^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 172.7 (C), 171.5 (C), 139.3 (CH), 116.4 (CH_2), 71.8 (CH_2), 55.0 (C), 52.8 (CH_3), 52.6 (CH_3), 42.8 (CH), 37.3 (C), 32.4 (CH_2), 31.5 (CH_2), 26.4 (CH_2), 14.9 (CH_3). HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{22}O_5Na$ $[M+Na]^+$: 293.1365, found: 293.1359.

Notes and references

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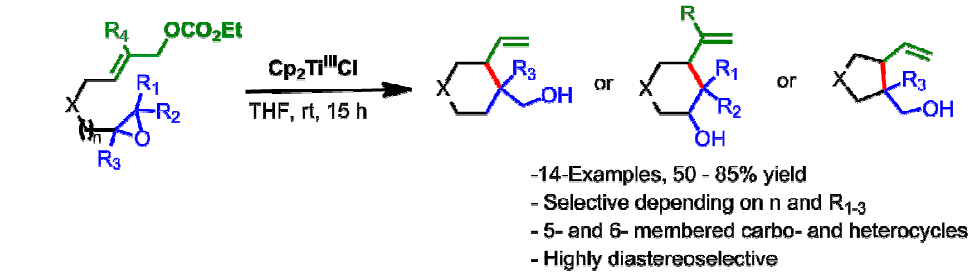
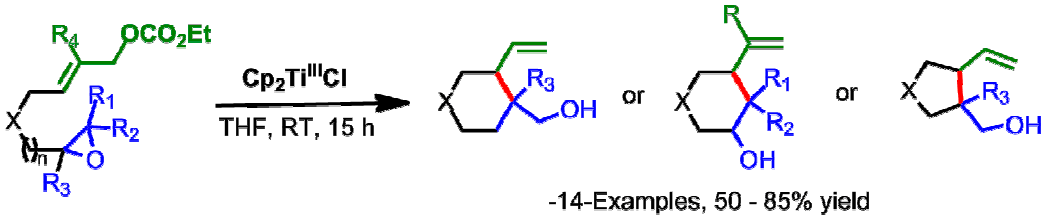
Diastereoselective synthesis of vinyl substituted carbo- and heterocyclic products is achieved by intramolecular radical cyclization of epoxy allyl carbonates



-14-Examples, 50 - 85% yield
- Selective depending on n and R_{1-3}
- 5- and 6- membered carbo- and heterocycles
- Highly diastereoselective



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