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Total synthesis of atropodiastereomers of heterodimeric *Amaryllidaceae* alkaloids: narcipavline and narcikachnine†‡

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We report the first asymmetric total synthesis of recently isolated heterodimeric *Amaryllidaceae* alkaloids, narcipavlines A (**1a**) and B (**1b**), and narcikachnines A (**2a**) and B (**2b**), thereby confirming their absolute stereochemistry. These alkaloids showcase a unique heterodimeric structure, amalgamating two distinct types of *Amaryllidaceae* alkaloids: the *cis*-hydrodibenzofuran containing tetracyclic galantamine core (**6a**) and the galanthindole core (**7**) featuring a biaryl axis. The presence of this biaryl axis, coupled with the substantial galantamine core (**6a**) at the *ortho* substituents, imposes constraints on free rotation around the C–C axis, resulting in atropisomerism, an exceedingly rare phenomenon in nature. Key steps in the synthesis encompass the utilization of a one-pot double reductive amination approach for the establishment of C–N–C bonds to merge both the galantamine (**6a**) and galanthindole (**7**) cores. Additionally, the Mitsunobu reaction and intramolecular Heck cyclization have emerged as pivotal techniques for crafting the tricyclic hydrodibenzofuran core [(–)-**13**], incorporating an all-carbon quaternary stereogenic center.

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Introduction

The *Amaryllidaceae* family, particularly plants in the *Narcissus* genus, have a rich history in traditional and Western medicine.¹ Dating back to the 4th century BC, famous Greek physician Hippocrates used extracted oil from *Narcissus poeticus* L. to treat uterine tumors. These plants are renowned for producing structurally and biologically significant *Amaryllidaceae* alkaloids² (AAs). The identification of lycorine in 1877 marked the start of an extraordinary voyage, leading to the discovery of over 600 AAs since then, highlighting a wide array of biological activities.^{2,3} Of particular interest are AAs with a *cis*-hydrodibenzofuran structure, featuring tetracyclic skeletons with *vicinal* quaternary and tertiary stereogenic centers, which show potential medicinal properties such as acetylcholinesterase (AChE) inhibition,^{4a} crucial in Alzheimer's disease (AD) treatment, as well as anti-malarial, anti-infective, and anti-cancer²

effects. *Amaryllidaceae* plants naturally synthesize these AAs from L-tyrosine through a series of oxidation and reduction reactions.³ Galantamine (**6a**), among the most well-known *Amaryllidaceae* alkaloids, has been utilized to treat mild to moderate Alzheimer's disease⁵ under the trade name Razadyne®, approved by the FDA in 2001. AD, a chronic and progressive neurodegenerative disorder, represents a significant global health concern affecting over 36 million individuals.⁶

Given the urgent need for effective therapies, research into novel treatments for AD is imperative. Currently all treatments of AD are only symptomatic aiming to boost acetylcholine levels through the inhibition of acetylcholinesterase using specific cholinesterase inhibitors like galantamine (**6a**), donepezil, and rivastigmine.⁷ An enzyme called butyrylcholinesterase (BuChE) is also able to hydrolyze AChE.⁸ Studies have indicated that in later stages of AD, patients experience a significant increase in butyrylcholinesterase levels by up to 50–70% while acetylcholinesterase expression decreases. This suggests that butyrylcholinesterase could be a promising therapeutic target, not only in restoring brain acetylcholine levels but also in serving as a disease-modifying agent in the prodromal stages of the disease.

Recently, a series of intricate heterodimeric *Amaryllidaceae* alkaloids have been freshly isolated (Fig. 1), showcasing atropodiastereomeric relationships. narcipavline (**1**) and narcikachnine (**2**) were isolated in 2018 from *Narcissus poeticus* cv. Pink Parasol,^{9a} existing as 1:1 and 1:1.2 diastereomeric

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Fig. 1 Dimeric atropodiastereomeric Amaryllidaceae alkaloids (1–5) and monomeric congeners (6–7) sharing a *cis*-hydrodibenzofuran core.

mixtures respectively. They are a combination of two structural types of Amaryllidaceae alkaloids: *cis*-hydrodibenzofuran containing lycoramine (6b) and bi-aryl axis containing galanthindole^{9c} (7) core (Fig. 1). Narcimatuline (3) was isolated from *Narcissus pseudonarcissus* bulbs,^{9b} existing as a 1 : 1.1 diastereomeric mixture, featuring a keto functionality at the *cis*-hydrodibenzofuran skeleton and *N*-methylindoline at the atropodiastereomeric position. Similar structural type narcielline (4) and narciabdule (5), isolated from *Zapharynthia citrina*^{10a} and *Narcissus pseudonarcissus*^{10b} respectively, in 2021, also exist as inseparable diastereomeric mixtures. While the stereochemistry and atropodiastereomerism were confirmed for narcielline (4) and narciabdule (5) by isolation chemists,^{10a} they still remained unclear for narcipavline (1) and narcikachnine (2). Therefore, we have proposed the structures of the diastereomeric mixture of narcipavline (1) as narcipavlines A (1a) and B (1b), and narcikachnine (2) as narcikachnines A (2a) and B (2b), considering them as naturally occurring atropodiastereomers. Importantly, these newly isolated alkaloids exhibit excellent BuChE inhibition, with narcipavlines (1) showing an IC₅₀ of 24.4 ± 1.2 μM, and narcimatulines (3) exhibiting an IC₅₀ of 5.90 ± 0.87 μM. Narcipavlines [*i.e.* narcipavlines A (1a) and B (1b)] also demonstrate antiplasmodial activity against malaria parasites, suggesting their potential for the development of new drugs. Biological activity for narcikachnines 2 [*i.e.* narcikachnines A (2a) and B (2b)] is yet to be discovered.

Structurally, these alkaloids possess three chiral centers, a *cis*-hydrodibenzofuran core, along with an all-carbon quaternary stereogenic center¹¹ and a chiral bi-aryl axis which also leads to complicated rare atropisomerism, makes them impressively challenging structures.¹² Atropisomerism, a form of dynamic chirality, occurs due to restricted rotation between the single bond between two sp²-hybridized atoms, yielding

atropisomers. These are classified into three categories, based on the rotational barrier (Δ*E*_{rot}) and half-life (*t*_{1/2}), class I (Δ*E*_{rot} < 20 kcal mol^{−1}, *t*_{1/2} ≈ ns-ms) with rapidly equilibrating conformers considered as achiral; class II (Δ*E*_{rot} ≈ 20–30 kcal mol^{−1}, *t*_{1/2} ≈ min-hours per days), considered high-risk in drug development due to moderate stability and class III high rotational barrier isomers (Δ*E*_{rot} > 30 kcal mol^{−1}, *t*_{1/2} ≈ years), highly stable and often developed as single atropisomers, although very challenging to synthesize.^{12b–e} Only very few syntheses have been reported for other atropodiastereomeric natural products.^{12a–d} Biosynthesis could be hypothesized from a combination of two different Amaryllidaceae alkaloids norlycoramine (6c) and galanthindole (7) *via* enzymatic alkylation, where both can be derived from L-tyrosine.³

Although there are many elegant approaches for the synthesis of galantamine (6a) and related tetracyclic scaffolds containing a *cis*-hydrodibenzofuran core,^{13–15} there has been no synthesis reported for the newly isolated complex heterodimeric Amaryllidaceae alkaloids to date. We hypothesized that classical reductive amination could be a useful tool to construct the C–N–C bond of the seven membered azepine ring in one pot and will be worth exploring in this regard. Due to their impressive biological activity and structurally challenging arrays, we envisioned a catalytic enantioselective unified approach *via* reductive amination to synthesize narcipavline (1) [*i.e.* the atropodiastereomers narcipavlines A (1a) and B (1b)] and narcikachnine (2) [*i.e.* the atropodiastereomers narcikachnines A (2a) and B (2b)] along with galantamine (6a) and lycoramine (6b).

Results and discussion

Retrosynthetically, narcikachnine (2) could be derived from narcipavline (1) *via* reduction of the indole ring. Narcipavline (1) consists of two parts: the northern part is the lycoramine core and southern part is a galanthindole (7) core. Initially, we envisioned accessing atropodiastereomers of narcipavline (1) [*i.e.* (1a) and (1b)] from an advanced intermediate 8 *via* allylic oxidation¹⁶ and hydrogenation (Scheme 1). To construct the



Scheme 1 Retrosynthetic analysis of narcipavline (1) and narcikachnine (2).



Scheme 2 Synthesis of galanthindolyl benzyl amine.

seven membered azepine core, a one-pot double reductive amination of galanthindolyl benzylamine (**12**) with tricyclic dialdehyde **10** was postulated (Scheme 1). The all-carbon quaternary stereogenic center¹¹ of tricycle **13** bearing an aldehyde and ester could be constructed *via* intramolecular Heck cyclization of alkyl aryl ether **14**, which further could be accessed *via* Mitsunobu reaction of the phenol derivative **15** with enantioenriched α -substituted cyclohex-2-en-1-ol **16** (Scheme 1).

Our journey commenced with the preparation of the galanthindole (**7**) core and its corresponding benzylic amine **12**. To this end, we synthesized the known biaryl aldehyde **17**, and galanthindole (**7**) following a modified procedure of Hsieh's protocol (see ESI† for details).¹⁷ Subsequently, we transformed the biaryl aldehyde **17** into the corresponding benzylamine ($\pm$)-**12** *via* a reductive amination using ammonium formate (Scheme 2).

The isolation chemists did not provide any optical rotation data for galanthindole (**7**).^{9c} However, due to its structural features, including a biphenyl axis and *ortho*-substituents, it can exhibit axial isomerism. Indeed, when subjected to HPLC analysis, galanthindole showed a 50 : 50 mixture of these two atropisomers, confirming its racemic nature [denoted as ($\pm$)-**7**]. For the synthesis of the galantamine core, we began with the synthesis of enantioenriched (96% ee) α -substituted cyclohex-2-en-1-ol¹⁸ **16** *via* a catalytic enantioselective Corey–Bakshi–Shibata (CBS) reduction¹⁹ of a known Trost's enone²⁰ [see ESI† for details].

Inspired by Banwell's protocol,^{14d} we explored the Mitsunobu reaction for the synthesis of enantioenriched **14**. Extensive optimization with different phosphines and azodicarboxylates revealed that allyl alcohol (+)-**16** (96% ee) and 2-iodophenol **15** afforded (–)-**14** in 93% ee in the presence of diethyl azodicarboxylate (DEAD) and tributylphosphine (^tBu₃P) [see ESI† for detailed optimization]. Gratifyingly, the stereochemistry of (–)-**14** was confirmed by single crystal X-ray analysis [CCDC 2384521].

With enantioenriched (–)-**14** (93% ee) in hand, we moved forward towards the intramolecular Heck cyclization to construct the *cis*-fused tricyclic hydrodibenzofuran core (Scheme 3). To our delight, charging iodoarene (–)-**14** under Heck coupling conditions using catalytic Pd(OAc)₂ smoothly afforded tricyclic product (–)-**13** with excellent dr (dr > 20 : 1), with generating the all carbon quaternary stereogenic centre. By employing our strategy, we have been able to achieve the hydrodibenzofuran core in 93% ee (see ESI† for HPLC analysis) in 4 steps from commercially available cyclohex-2-en-1-one which is superior to the previous reports.^{13b–d,14d} Further, lithium aluminium hydride reduction of the ester group of **13**

followed by oxidation using Dess–Martin periodinane (DMP) afforded di-aldehyde (–)-**10** in 85% yield over 2 steps (Scheme 3).²¹ A one step reduction using DIBAL–H proved to be difficult as it is associated with over-reduced diol in 35% yield in addition to the desired dialdehyde **10** (see ESI† for details).²¹ Next, reacting equimolar amounts of dialdehyde (–)-**10** and benzylamine ($\pm$)-**12** in the presence of sodium cyanoborohydride (NaBH₃CN) and a catalytic amount of trifluoroacetic acid afforded the desired product (–)-**8** in 84% yield (Scheme 3). Interestingly, ¹H NMR analysis of the pure product revealed the presence of two diastereomers in a ~1 : 1 ratio, attributable to atropisomerism around the biphenyl axis, resulting in two distinct configurations of atropodiastereomers **8a** and **8b** (Scheme 3). The separation of these atropodiastereomers was a tedious job, as the TLC shows a single spot, making them inseparable in column chromatography.

At this stage, only a diastereoselective allylic oxidation was required to complete the total synthesis of narcipavlines (**1**). However, all efforts to perform allylic oxidation were unsuccessful and seemed to be very challenging (Scheme 3). When the mixture of **8a** and **8b** was charged under allylic oxidation conditions using selenium dioxide and TBHP, it was observed that the indole ring of **8** is highly susceptible to oxidation compared to the allylic position. Even under mild conditions using selenium dioxide and *tert*-butyl hydrogen peroxide

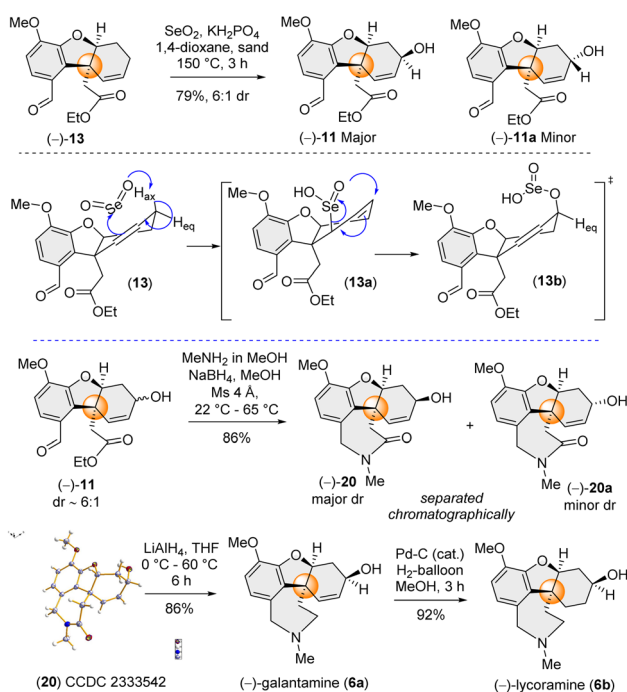


Scheme 3 Forward synthesis towards narcipavline.

(TBHP), we could observe the formation of ~1 : 1 atropodiastereomers of 2-oxindoles, **18a** and **18b** (Scheme 3). Therefore, we recognized the necessity of installing the allylic alcohol early in the tricyclic core (–)-**13**.

Therefore, employing Trost's procedure,^{13c} we successfully executed the allylic oxidation of (–)-**13** using selenium dioxide (SeO₂) with sand as a solid support in refluxing 1,4-dioxane to afford a mixture of **11** and **11a** (79% yield, dr ~6 : 1 in favour of **11**) (Scheme 4). The diastereoselectivity observed in case of allylic oxidation was attributed to the approach of SeO₂ from the non-traditional more hindered concave face of tricycle (–)-**13** (Scheme 4). The mechanism involves an Ene-type reaction and the stereoelectronic requirements of the Ene reaction dictate specific spatial arrangements, where approach through the pseudo-axial H rather than the pseudo-equatorial H of cyclohexene results in the formation of **11** as the major diastereomer (Scheme 4).

Next, we focused on the one-pot reductive amination-lactamization sequence of aldehyde and ester groups present in (–)-**11** (Scheme 4). It was observed that (–)-**11** (~6 : 1 dr) in the presence of MeNH₂ in MeOH followed by reduction using NaBH₄ afforded lactams (–)-**20** (as the major dr) and **20a** (see ESI† for details). Gratifyingly, these two diastereomers were separable in column chromatography. The structure of major diastereomer **20**, having the hydroxyl group above the plane, was confirmed by X-ray single crystal analysis (CCDC 2333542). Next, with tetracycle (–)-**20** in hand, we completed the total synthesis of naturally occurring (–)-galantamine [(–)-**6a**] just by LiAlH₄ reduction (86% yield). Further, hydrogenation of (–)-**6a** completed the total synthesis of (–)-lycoramine [(–)-**6b**].



Scheme 4 Diastereoselective allylic oxidation and synthesis of (–)-galantamine (**6a**) and (–)-lycoramine (**6b**).

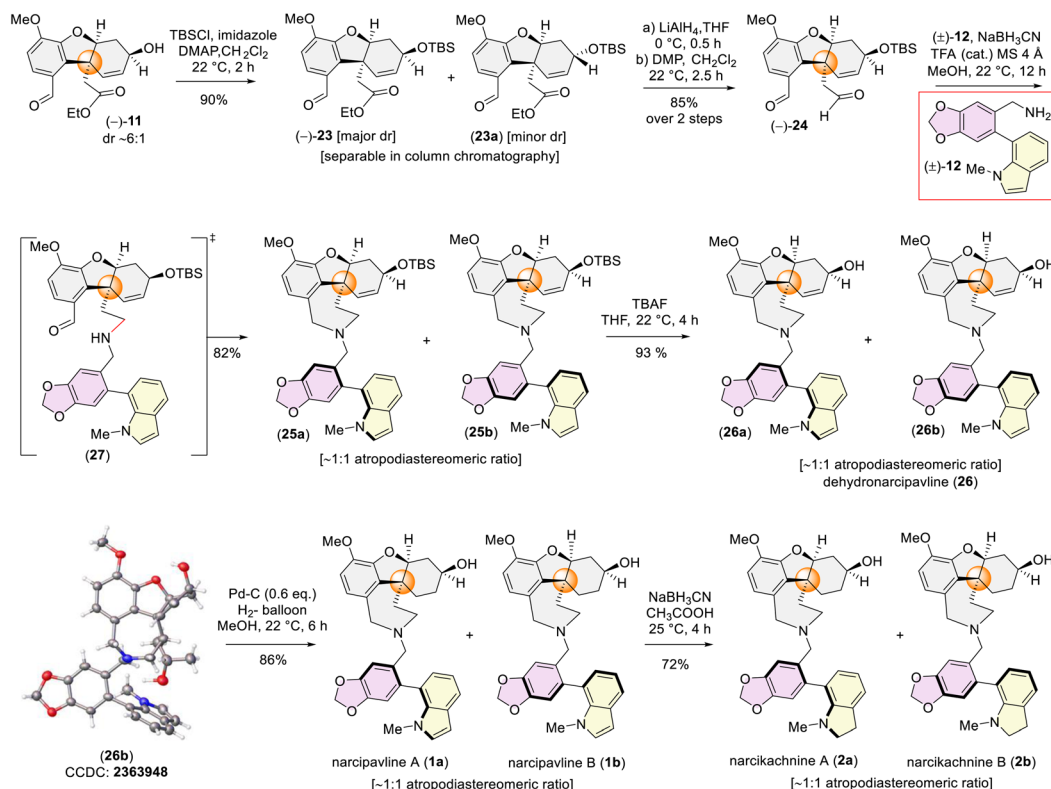


Scheme 5 Failed attempt towards reductive amination lactamization with galanthindolyl benzylic amine.

We next turned our attention to the synthesis of the azepine core of narcipavline (**1**) *via* a similar one-pot reductive amination-lactamization cascade. However, this proved to be very challenging with the sterically demanding benzylamine ($\pm$)-**12** (Scheme 5).

A condensation reaction of (–)-**11** with benzylamine **12**, followed by reduction using NaBH₄ didn't afford the required azepine core; instead, we could isolate benzyl alcohol **21** and ϵ -lactone **22** (through acid-catalysed cyclization) in a few specific cases (Scheme 5). This fact is probably attributed to the strongly electron-donating nature of the *p*-methoxy group on (–)-**11** which could diminish the electrophilicity of benzaldehyde hindering the crucial imine formation (Scheme 5).

So, we first protected the secondary alcohol group of **11** as TBS-ether to access (–)-**23** and (–)-**23a** (Scheme 6). Delightfully, we could separate the major diastereomers **23** *via* column chromatography. Next, the ester and the aldehyde group both were reduced and again re-oxidized using Dess–Martin periodinane (DMP) to afford dialdehyde (–)-**24** in 85% yield over 2 steps (Scheme 6). Subsequently, a one-pot sequential reductive amination was successfully conducted with (–)-**24** and galanthindolyl benzylamine ($\pm$)-**12** in the presence of NaBH₃CN and catalytic trifluoroacetic acid to furnish **25** as a mixture of two atropodiastereomers, **25a** and **25b** with dr ~1 : 1 (see ESI† for detailed characterization). Next, deprotection of the silyl ether group was achieved using *tetra*-butyl ammonium fluoride (TBAF) yielding dehydronarcipvaline (**26a** and **26b**) as 1 : 1 atropodiastereomers. It is pertinent to mention that, a racemic crystal structure of ($\pm$)-**26b** (CCDC 2363948) (prepared from ($\pm$)-**24** in a different sequence) unequivocally proved the all-bond connections present in dehydronarcipvaline **26**. With a few milligrams of crystals in hand, a detailed ¹H-NMR analysis was undertaken. It is interesting to note that the ¹H-NMR of ($\pm$)-**26b** showed the signals for a single atropodiastereomer (see ESI† for details). However, when ¹³C-NMR of ($\pm$)-**26b** was recorded after a day (~24 h), the signal of each carbon appeared to be doubled, thereby confirming the rotation along the axis happening at room temperature. Further, the ¹H-NMR of the same sample after ~24 h provided the signals for ~1 : 1 atropodiastereomers [($\pm$)-**26a** and ($\pm$)-**26b**]. Thus, it may be concluded that the atropodiastereomer ($\pm$)-**26b** has a very short half-life period and could be easily converted to ($\pm$)-**26a**, leading



Scheme 6 Total synthesis of atropodiastereomers narcipavline A, B and narcikachnine A, B.

to the mixtures of atropodiastereomers at room temperature (see ESI† for details).

Next, the atropodiastereomers of dehydronarcipavline **26** (~1:1 dr) were hydrogenated using Pd-C at 1 atm. H_2 -gas afforded the first total synthesis of atropodiastereomers of novel heterodimeric *Amaryllidaceae* alkaloids, narcipavlines A (**1a**) and B (**1b**) as ~1:1 dr (Scheme 6). Efforts towards the separation of the atropodiastereomers proved to be unsuccessful at room temperature using column chromatography. Nevertheless, all the corresponding peaks of ^1H - and ^{13}C -NMR are in good agreement with the isolation report of narcipavlines (**1a**: **1b** ~1:1) by Cahliková *et al.*^{9a} The structure was confirmed through 2D NMR analysis, which revealed a negative specific rotation value for the diastereomeric mixture. Notably, compound **1** and lycoramine (**6b**) exhibited similar NMR spectra, particularly in the region of the secondary alcohol within the *cis*-hydrodibenzofuran core, and displayed negative optical rotation values. Further, HPLC analysis using a Chiralpak OD-H column (40% *i*PrOH/*n*-hexane) revealed two pairs of enantiomers [93% ee] corresponding to the atropodiastereomers narcipavlines A (**1a**) and B (**1b**) [~50:50 ratio] (see ESI† for details). These findings strongly support the proposed structure of atropodiastereomers **1a** and **1b**, resembling (*-*)-lycoramine (**6b**) as a *cis*-hydrodibenzofuran core, where the secondary alcohol group resides above the plane (Fig. 1).

We next turned our attention to the total synthesis of atropodiastereomeric alkaloids, narcikachnines A (**2a**) and B (**2b**) (Scheme 6). Their structures are nearly identical, with the sole

difference being an indoline ring in narcikachnine (**2**) instead of an indole in narcipavline (**1**). After a quick optimization, we were pleased to see that the indole ring of narcipavline (**1**) could be reduced with NaBH₃CN in AcOH to form indolines of narcikachnines A (**2a**) and B (**2b**) in 72% yield in ~1:1 dr (Scheme 6). A plausible mechanism of reductive amination of indole to indoline is shown in Scheme 7.

Once again, all the corresponding peaks of ^1H - and ^{13}C -NMR are in good agreement with the isolation report of narcikachnines (**2a**: **2b** ~1:1) by Cahliková *et al.*^{9a} The diastereomeric mixture of narcikachnines (**2a**: **2b**) shows a negative specific rotation value. The cause of the doubling of some signals in NMR was found to be due to axial isomerism through the sterically hindered single bond rotation. Accordingly, VT NMR analysis was performed to demonstrate the atropodias-tereomerism at different temperatures. Few milligrams of (**2**) and (**26**) were dissolved in DMSO-*d*₆ having a sufficiently high boiling point. At the highest experimental temperature, (up to



Scheme 7 Probable mechanism for the reduction of the indole ring.



Galantindole **7** presents an intermediate energy barrier, with TS₁ at 25.09 kcal mol⁻¹ and TS₂ at 30.78 kcal mol⁻¹, reflecting a balance between flexibility and rigidity. The energy peaks at TS₁ and TS₂ indicate that **7** experiences moderate steric hindrance during rotation. This intermediate behaviour may allow for the possibility of selectively separating the distinct conformers (*S*)-**7**, (*R*)-**7**, and (*S*)-**7'**, however under very special circumstances.

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