

Concise Total Synthesis of Lundurines A–C Enabled by Gold Catalysis and a Homodienyl Retro-Ene/Ene Isomerization

Maria S. Kirillova,[†] Michael E. Muratore,[†] Ruth Dorel,[†] and Antonio M. Echavarren^{*,†,‡}

[†]Institute of Chemical Research of Catalonia (ICIQ), Barcelona Institute of Science and Technology, Av. Paisos Catalans 16, 43007 Tarragona, Spain

[‡]Departament de Química Orgànica i Analítica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, 43007 Tarragona, Spain

S Supporting Information

ABSTRACT: The total synthesis of lundurines A–C has been accomplished in racemic and enantiopure forms in 11–13 and 12–14 steps, respectively, without protection/deprotection of functional groups, by a novel tandem double condensation/Claisen rearrangement, a gold(I)-catalyzed alkyne hydroarylation, a cyclopropanation via formal [3 + 2] cycloaddition/nitrogen extrusion, and a remarkable olefin migration through a vinylcyclopropane retro-ene/ene reaction that streamlines the endgame.

Lundurines A (1), B (2), and C (3) were isolated from *Kopsia tenuis*,¹ a plant endemic to the north of Borneo, and show interesting cytotoxicity.² These alkaloids feature a unique indoline-fused polyhydropyrroloazocine and cyclopropyl moiety fused to the indoline (Figure 1). Related alkaloids lacking the cyclopropane ring, such as lapidilectam, lapidilectines, grandilodines, and tenuisines, have also been isolated from plants of the *Kopsia* genus.³

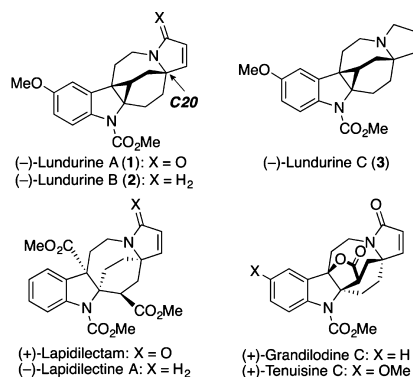
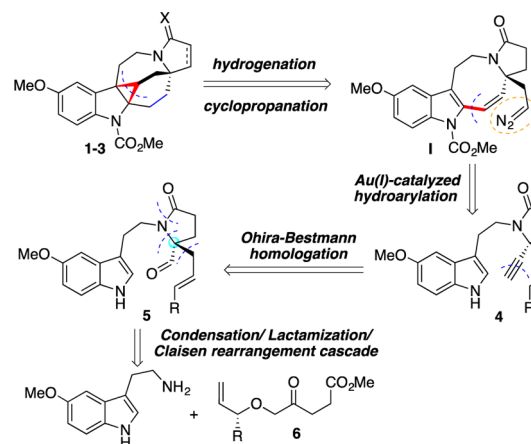


Figure 1. Lundurines A–C and related alkaloids.

The lundurines have recently attracted considerable attention,⁴ and the total syntheses of lundurine A and lundurine B have been reported.^{4b–f} However, all previous approaches were lengthy, involving over 20 linear synthetic steps, thus making the synthesis of large quantities of the natural products and/or analogues, for broad biological assays, inconvenient.^{4b–f} We now report the expedient total synthesis of the three members of the lundurine family, including the first total synthesis of racemic and enantiopure lundurine C, by constructing the key lactam

intermediate 4 in a single step by a condensation/Claisen rearrangement followed by a gold(I)-catalyzed intramolecular hydroarylation to form the 8-membered ring⁵ (Scheme 1). In our

Scheme 1. Retrosynthetic Approach



initial plan, we expected that a transition-metal-catalyzed reaction of a carbene precursor of type I would lead to intramolecular cyclopropanation of the indole nucleus. However, a more effective solution was found using an acid-catalyzed pyrazoline formation. The endgame relied on an unexpectedly facile vinylcyclopropane retro-ene/ene reaction that led to alkene migration, streamlining the culmination of the synthesis.

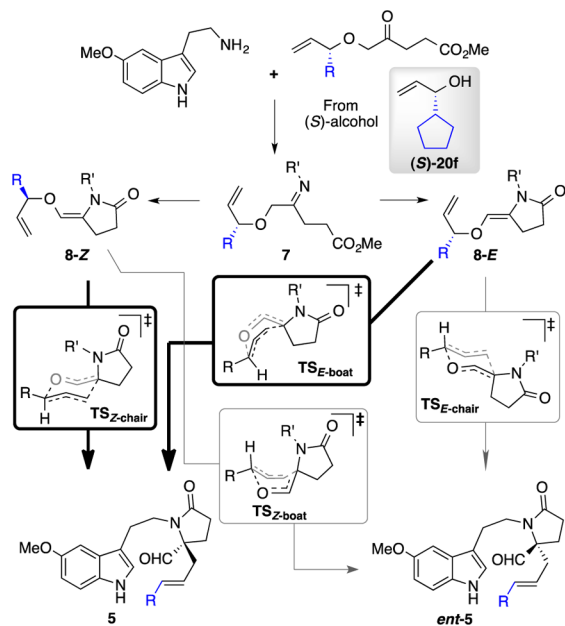
For the synthesis of key chiral intermediate 5, we envisioned condensing oxoester 6 with commercially available 5-methoxytryptamine. This should lead to imine 7, which should undergo lactamization to form pyrrolidinones 8-Z and 8-E. Ultimately, 8-Z and 8-E could afford 5 through a Claisen rearrangement.⁶ For the enantioselective synthesis of 4, we proposed building the C20 stereocenter by enantiodiscrimination through transfer of chirality in the Claisen rearrangement (Scheme 2).

Examples of efficient transfer of chirality on flexible systems featuring a “traceless” chiral auxiliary on the allyl fragment, and in the absence of a Lewis acid, are scarce.⁷ Nonetheless, we prepared a range of (S)-chiral alcohols by enzymatic resolution of the racemic allylic alcohols,⁸ which were converted into the desired chiral oxoesters 6 in a single step. The best transfer of

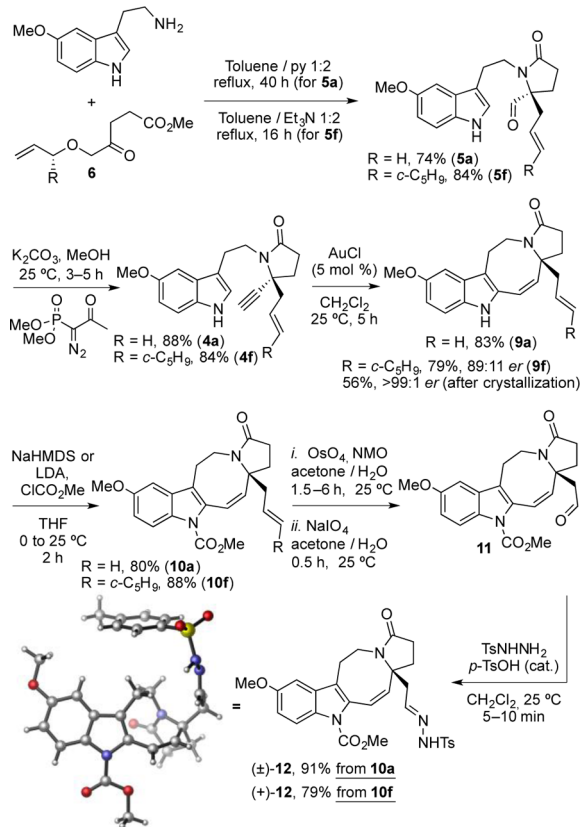
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Scheme 2. Enantioselective Claisen Rearrangement



chirality was achieved with $R = c\text{-pentyl}$ (89:11 *er*). It is important to note that the use of basic conditions turned out to be essential to avoid the Pictet–Spengler type reaction that would form tetrahydro β -carbolines.⁹ Thus, mixtures of pyridine/toluene or Et_3N /toluene proved to be optimal, affording high yields of lactam ($R = \text{H}$: 5a 74%; $R = c\text{-pentyl}$, 5f 84%) (Scheme 3).

Scheme 3. Synthesis of (+)-9f and Hydrazone (+)-12^a

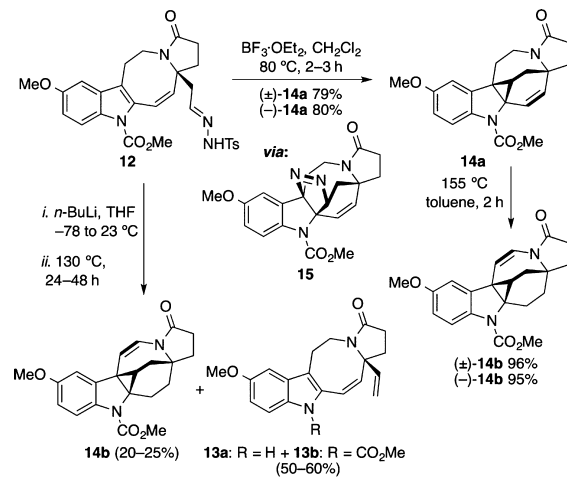
^aCYLview depiction of the X-ray crystal structure of (+)-12.

Initially, we had expected that the system would be under Curtin–Hammett conditions, as a result of a fast equilibrium between 8-Z and 8-E. However, in a closely related model system, we isolated the *E*- and *Z*-pyrrolidinones (2.6:1 ratio), which did not undergo equilibration after being heated at 100 °C in 1:2 toluene– Et_3N for several hours.¹⁰ Presumably, the major 8-*E* pyrrolidinone reacts preferentially through a boat-like transition state $TS_{E\text{-boat}}$ to form (*S*)-5, whereas the minor isomer 8-*Z* reacts through $TS_{Z\text{-chair}}$ (Scheme 2).¹¹

Aldehyde 5 was immediately homologated into the corresponding alkyne 4 employing the Ohira–Bestmann reagent (4a 88%; 4f 84%, 89:11 *er*), setting the stage for the key 8-*endo*-dig gold(I)-catalyzed hydroarylation (Scheme 3). This was accomplished with perfect 8-*endo* selectivity with 5 mol % AuCl (9a 83%; 9f 79%, 89:11 *er*). Compound 9f was crystallized to obtain virtually enantiopure material (mother liquor, 56%, > 99:1 *er*). The methyl carbamate at the indole nitrogen was then introduced (10a 80%; 10f 88%), and the exocyclic olefin was converted to the corresponding aldehyde via a dihydroxylation/oxidative cleavage sequence, that was performed in one pot. Although aldehyde 11 may be isolated, it was routinely converted without further purification into tosyl hydrazone 12 ((\pm) -12, 91% and (+)-12, 79% from 10). The absolute configuration of (+)-12 was determined by single crystal X-ray diffraction, confirming the C20 (*S*)-configuration of all previous intermediates.

Initial attempts to form 14a by various transition-metal-catalyzed procedures^{4f} were unsuccessful. However, 14b was formed through deprotonation of the hydrazone and generation of the corresponding diazo compound, although we were not able to obtain yields higher than 20–25%, the main products being the undesired vinyl-substituted tetracycles 13a–b (Scheme 4). Most surprising was the fact that in 14b^{12,13} the

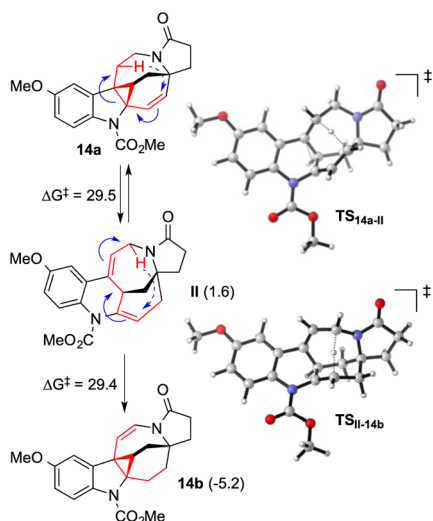
Scheme 4. Indole Cyclopropanation and Olefin Isomerization



double bond had migrated to the opposite side of the hexahydroazocine ring. We also isolated pyrazoline 15,¹² which is the first example of a formal [3 + 2] dipolar cycloaddition between a diazocompound and an indole. By performing a formal [3 + 2] cycloaddition of tosyl hydrazone 12 in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ as the Lewis acid,¹⁴ we obtained 14a in 79–80% yield. Remarkably, this product of direct cyclopropanation (14a) could be converted in essentially quantitative yield into its isomer 14b by simple heating at 155 °C for 2 h.

The puzzling isomerization of **14a** most likely proceeds by a homodienyl retro-ene rearrangement¹⁵ via 1,4-diene **II**, followed by the reverse process to form **14b** (Scheme 5). This type of

Scheme 5. Migration of the Olefin from **14a** to **14b** via Homodienyl Retro-Ene/Ene Rearrangement^a

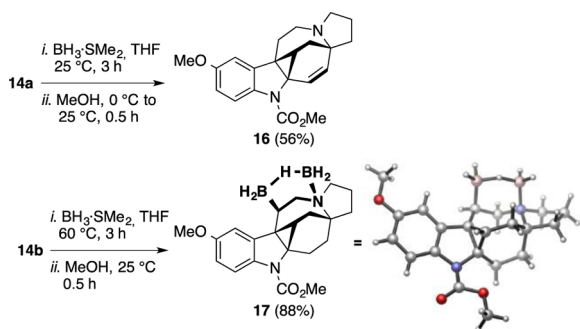


^aNumbers in parentheses correspond to relative free energies in kcal·mol⁻¹ (B3LYP/6-31G(d), solvent = toluene).

transformation has been studied before in cyclic and bicyclic systems, leading irreversibly to skipped dienes.¹⁶ The homodienyl retro-ene rearrangement of bicyclo[5.1.0]octen-2-ene has been reported to take place at 150–170 °C, to furnish 1,4-cyclooctadiene with an activation energy of *ca.* 33 kcal·mol⁻¹.^{16d} The reverse process, the formation of vinyl cyclopropanes from skipped dienes under thermal conditions, has only one precedent in the oxy-homodienyl rearrangement, which requires a temperature of *ca.* 260 °C (activation energies of 41–43.5 kcal·mol⁻¹).¹⁷ However, according to DFT calculations, the two transition states for the hydrogen shifts in our system have much lower barriers (*ca.* 29.5 kcal·mol⁻¹) and the formation of a more stable conjugated enaminone drives the equilibrium toward the formation of **14b**.¹⁸

Isomers **14a** and **14b** behave very differently in their reactions with borane. Thus, whereas **14a** reacted with excess BH₃·SMe₂ by exclusive reduction of the lactam to give **16** (56%), **14b** led to an unexpected and remarkably inert heptacyclic diborane **17** (Scheme 6).

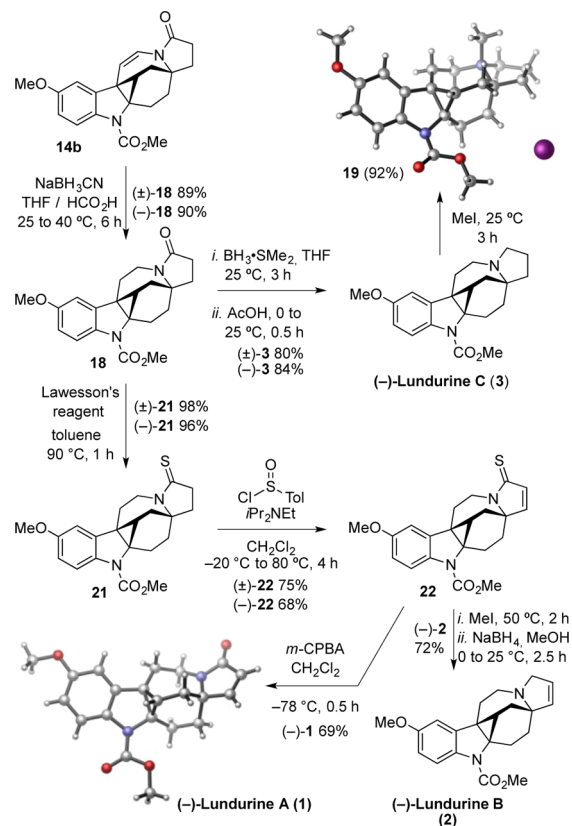
Scheme 6. Reduction of **14a–b** with Borane^a



^aCYLview depiction of the X-ray crystal structure of (±)-17.

Hydrogenation of **16** using PtO₂ as the precatalyst gave lundurine C (**3**), albeit in a rather low yield (44%), while hydrogenation of the olefin of **14a** prior to borane reduction of the lactam was unsuccessful. Gratifyingly, the ready access to **14b** led to a considerably more efficient synthesis of **3** and, more importantly, provided an entry to the synthesis of lundurines A (**1**) and B (**2**). Hence, the first total synthesis of **3** could be completed in two steps from **14b**, by reduction of the enaminone double bond with NaBH₃CN¹⁹ in the presence of formic acid to form saturated lactam **18**, followed by a second reduction with BH₃·SMe₂ (Scheme 7). Surprisingly, enantiopure lundurine C

Scheme 7. Synthesis of Lundurines A–C^a



^aCYLview depictions of the X-ray crystal structures of iodide salt **19** and lundurine A ((-)-1), with absolute configurations.

(**3**) presented an optical rotation ($[\alpha]_D^{589} = -1.1 \pm 0.6^\circ$, CHCl₃, *c* 0.98, 300 K) and ($[\alpha]_D^{589} = -6.2 \pm 0.8^\circ$, CH₂Cl₂, *c* 0.3, 301 K]) differing significantly from the one reported for the natural product ($[\alpha]_D^{589} = -25^\circ$, CHCl₃, *c* 0.067),^{1,2} although chiral HPLC analysis of our synthetic sample of lundurine C left no doubt with regards to its enantiopurity. Furthermore, we prepared crystalline quaternary ammonium iodide **19**, whose absolute configuration was established by X-ray crystallography. The discrepancy in the value of the optical rotation may arise from the very low concentration at which the natural product was measured originally that induced a significant error in the measurement.

Lundurines A (**1**) and B (**2**) were both prepared in three additional steps from **18**, by thiolation/*C*-sulfonylation–elimination and either oxidation or reduction (Scheme 7). Intermediate **18** was first subjected to Lawesson's reagent to form thiolactam **21**, which then reacted with *p*-toluenesulfonyl chloride, in the presence of Hünig's base, to generate *in situ* an α -

sulfinyl thiolactam.²⁰ Upon heating at 80 °C, a Cope-type elimination gave thiolundurine A (**22**). Oxidation of **22** with m-CPBA at -78 °C produced (-)-lundurine A (**1**) in 69% yield, while treatment of **22** with iodomethane followed by sodium borohydride gave (-)-lundurine B (**2**) in 72% yield. Interestingly, unlike stated in the isolation and previous syntheses, racemic and enantiopure **1** are crystalline solids and we have also obtained the crystal structure of this natural product, confirming its absolute configuration and the one of the whole family of natural compounds.

In conclusion, we have developed a unified approach toward the synthesis of lundurines A–C, including the first enantioselective total synthesis of lundurine C, taking advantage of a gold(I)-catalyzed 8-*endo*-dig selective hydroheteroarylation to build the polyhydroazocine ring. Our synthesis of the lundurines is the shortest and most efficient to date (12–14 steps from known chiral alcohol **20f**,²¹ 6.6% overall yield for lundurine C and 3% overall yield for lundurines A and B, >99:1 *er*) and is perfectly suited to the preparation of analogues for biological evaluation as well as its extension to the synthesis of other *Kopsia* alkaloids. Worthy of note is the implementation of a practical chirality transfer in a complex tandem transformation and the new intramolecular cyclopropanation of indoles by formation of a pyrazoline by formal [3 + 2] cycloaddition in the presence of a Lewis acid. Finally, as often encountered in total synthesis endeavors, serendipity also played a significant role in the discovery of a new transformation in which a double bond migrates by means of a homodienyl retro-ene/ene rearrangement, which streamlined the access to this family of alkaloids.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01428.

Crystallographic data files (ZIP)

All procedures and characterization data for compounds **1–3**; **4a,f–6a,f**; **9a,f–10a,f**; and **11–22** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*aechavarren@iciq.es

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Kam, T.-S.; Yoganathan, K.; Chuah, C. H. *Tetrahedron Lett.* **1995**, *36*, 759–762.
- (2) Kam, T.-S.; Lim, K.-H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739–10745.
- (3) (a) Awang, K.; Sévenet, T.; País, M.; Hadi, A. H. A. *J. Nat. Prod.* **1993**, *56*, 1134–1139. (b) Yap, W.-S.; Gan, C.-Y.; Low, Y.-Y.; Choo, Y.-

M.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2011**, *74*, 1309–1312.

- (4) (a) Schultz, E. E.; Pujanauski, B. G.; Sarpong, R. *Org. Lett.* **2012**, *14*, 648–651. (b) Hoshi, M.; Kaneko, O.; Nakajima, M.; Arai, S.; Nishida, A. *Org. Lett.* **2014**, *16*, 768–771. (c) Arai, S.; Nakajima, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5569–5572. (d) Jin, S.; Gong, J.; Qin, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 2228–2231. (e) Nakajima, M.; Arai, S.; Nishida, A. *Chem. - Asian J.* **2015**, *10*, 1065–1070. (f) Huang, H.-X.; Jin, S.-J.; Gong, J.; Zhang, D.; Song, H.; Qin, Y. *Chem. - Eur. J.* **2015**, *21*, 13284–13290.

- (5) (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105–1109. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. - Eur. J.* **2007**, *13*, 1358–1373. (c) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015–9020.

- (6) (a) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1427–1428. (b) Desmaële, D.; Champion, N. *Tetrahedron Lett.* **1992**, *33*, 4447–4450. (c) Deyine, A.; Poirier, J.-M.; Duhamel, P. *Synlett* **2008**, 260–262.

- (7) (a) Pandey, G.; Khamrai, J.; Mishra, A. *Org. Lett.* **2015**, *17*, 952–955. (b) Zhang, Q.-Q.; Xie, J.-H.; Yang, X.-H.; Xie, J.-B.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 6158–6161. (c) Güneş, Y.; Polat, M. F.; Sahin, E.; Fleming, F. F.; Altundas, R. *J. Org. Chem.* **2010**, *75*, 7092–7098.

- (8) Štambaský, J.; Malkov, A. V.; Kočovský, P. *J. Org. Chem.* **2008**, *73*, 9148–9150.

- (9) (a) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797. (b) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720–4723.

- (10) To simulate the real reaction conditions, we added *ca.* 1 equiv of MeOH and 2 equiv of water. See [Supporting Information](#).

- (11) Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N. *J. Org. Chem.* **2003**, *68*, 572–577.

- (12) See [Supporting Information](#) for the X-ray structure.

- (13) (a) The absolute structure high resolution data were collected using Molybdenum radiation and applying methodology described in: Escudero-Adán, E. C.; Benet-Buchholz, J. B.; Ballester, P. *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.* **2014**, *70*, 660–668. The absolute configuration was determined reliably with a Flack^{13b} value based on Parsons' quotients^{13c} of the 0.00(8) R1 value for the structure of 2.86%. (b) Flack, H. D. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1983**, *39*, 876–881. (c) Parsons, S.; Flack, H. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2004**, *60*, S61.

- (14) (a) Frank, É.; Mucsi, Z.; Zupkó, I.; Réthy, B.; Falkay, G.; Schneider, G.; Wölfling, J. *J. Am. Chem. Soc.* **2009**, *131*, 3894–3904. (b) Padwa, A.; Ku, H. *J. Org. Chem.* **1980**, *45*, 3756–3766. (c) Schultz, A. G.; Eng, K. K. *Tetrahedron Lett.* **1986**, *27*, 2331–2334.

- (15) Hudlicky, T.; Koszyk, F. *J. Tetrahedron Lett.* **1980**, *21*, 2487–2490.

- (16) (a) von E. Doering, W.; Roth, W. R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 115–122. (b) Ellis, R. J.; Frey, H. M. *Proc. Chem. Soc.* **1964**, 221. (c) Grimme, W. *Chem. Ber.* **1965**, *98*, 756–763. (d) Glass, D. S.; Boikess, R. S.; Winstein, S. *Tetrahedron Lett.* **1966**, *7*, 999–1008. (e) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1650–1652. (f) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 4595–4606.

- (17) Klärner, F.-G.; Rüngeler, W.; Maifeld, W. *Angew. Chem.* **1981**, *93*, 613–614.

- (18) A dyotropic rearrangement of **14a** into **14b** is highly unlikely, since the computed barrier of activation for this process would be very high (>80 kcal·mol⁻¹). See [Supporting Information](#).

- (19) Yazici, A.; Pyne, S. G. *Org. Lett.* **2013**, *15*, 5878–5881.

- (20) Magnus, P.; Pappalardo, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 212–217.

- (21) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691.