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Structure and reactivity of a chiral cyclononadienone

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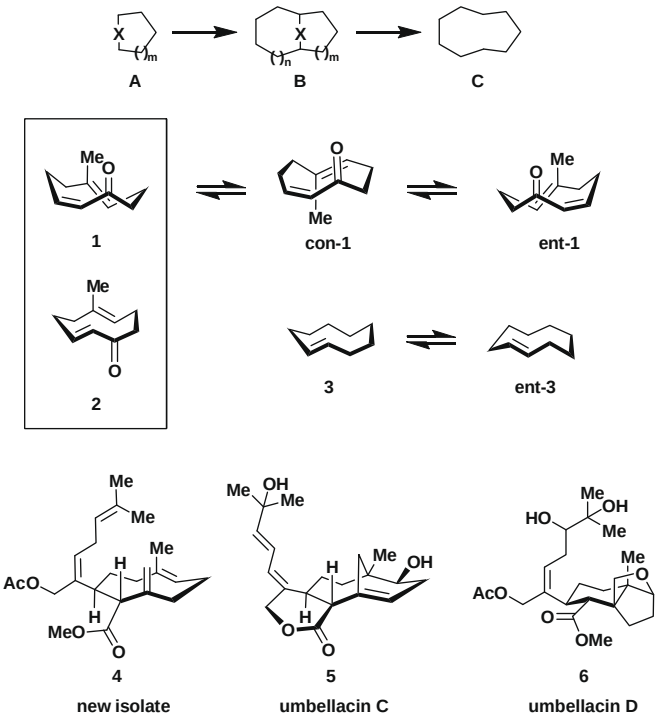
ABSTRACT

The structure and reactivity of a highly enantioenriched dissymmetric cyclononadienone are described.

The problem of the synthesis of nine-membered cycloalkanes primarily stems from destabilizing trans-annular interactions.[1] Most synthetic strategies to prepare cyclononanes and their derivatives deal with this structural congestion by initial formation of a smaller ring to which a second ring is then fused (**A**→**B**, Scheme 1).[2] In a subsequent maneuver, the small ring connectivity is removed and the nine-membered ring connectivity is left intact (**B**→**C**). The related strategy of temporary macrocycle formation and then ring contraction to give a nine-membered ring is also known.[2b] The 1964 and 2008 chemical syntheses of β-caryophyllene by Corey and coworkers constitute the first and most recent preparation of this nine-membered ring-containing natural product and demonstrate the logic represented in **A**→**B**→**C**.[3] The 2008 synthesis utilized ketone **1**. Here, we describe our studies related to the structure and reactivity of (−)-cyclononadienone **1**, a nine-membered ring-containing molecule that lacks the archetypal stereogenic center or axis of chirality but is, nevertheless, chiral.

Our interest in the synthesis of nine-membered ring-containing natural products was piqued by the recognition that strategies to access such targets are lacking. We were further attracted to this problem by reports of isolates, for example, **4**, from the soft coral *Xenia elongata* identified through the use of a novel assay for apoptotic activity in cancer cells.[4] Most of the molecules in this class, including those that lack an isolated nine-membered ring, as in umbellacins C (**5**) and D[5] (**6**), have not been studied in detail due to the paucity of materials obtained from the organisms that produce them coupled with the difficulty associated with their chemical synthesis.

Cope and others recognized that in order for *trans*-cyclononene and related ring systems to racemize, they must undergo a potentially slow conformational interconversion (**3**→**ent-3**).[6] This



Scheme 1.

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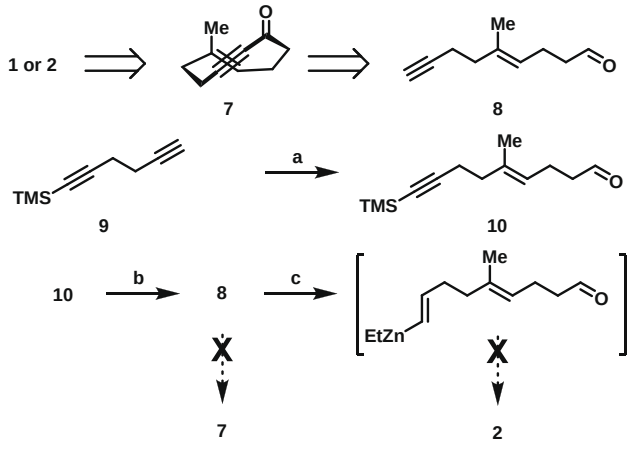
substance was shown to have a racemization half-life of approximately 4 min at 0 °C, and 6 s at 25 °C. We wondered if more functionalized constructs, for example, **1** and analogous structures (e.g., **2**), would racemize more slowly than the parent compound. In the case of **1**, the racemization process could well be step-wise, for example, conversion of **1** to **con-1** and then to **ent-1**. In favorable cases, species such as **1** could be prepared directly in enantioenriched form or resolved by dynamic kinetic methods. Importantly, stereoselective transformations of this substance should be possible when racemization is slow. Hence, this strategy aims to convert traditional chirality into conformational chirality[7] and then to new center chirality.

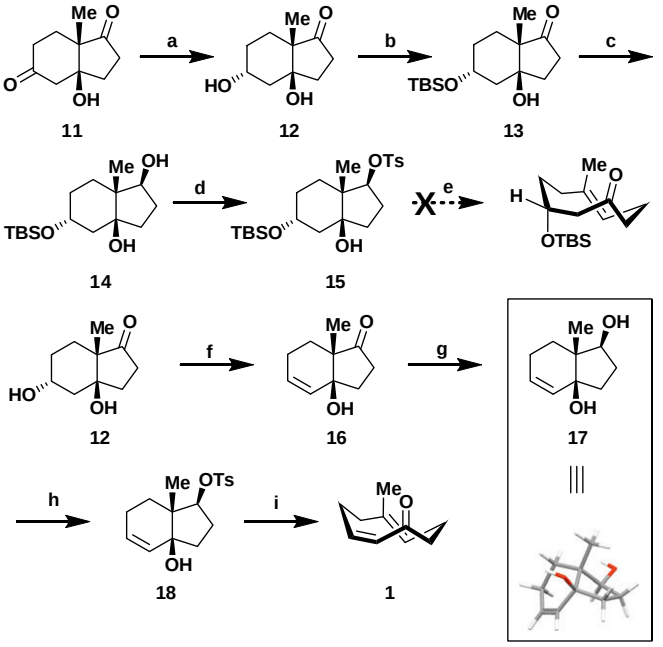
We prepared **1** and initiated the study of its structure and reactivity. Originally, our synthesis focused on direct cyclization of an acyclic precursor (**8**, Scheme 2). The presence of the trans-olefin in **10** complicates this strategy, since the olefin geometry necessarily projects the termini in opposite directions. Still, this route benefits from avoidance of transannular strain. The single flask conversion of known diyne **9** by way of a carbometalation/transmetalation/conjugate addition sequence[8] gave ynal **10** (30%, unoptimized). Unfortunately, cyclization of the desilylated ynal gave complex mixtures of products that did not include the desired cyclononenes (**8**→**2, 7**).

An alternative route to enantioenriched **1** is shown in Scheme 3. Use of ketone **11** followed by eventual fragmentation would enable access to enones of type **1**. At the outset of this work, it was unclear that the dissymmetric structure would be sufficiently stable to be converted stereoselectively to enantioenriched products; however, this route coincided with that of Corey and Lavinov in their elegant (and stereoselective!) syntheses of caryophyllene and coriaxeniolide.[3c] Briefly, ketone **11** was prepared in enantioenriched form,[9] reduced, protected, reduced again (→**14**), and then activated for fragmentation (→**15**).[10] Tosylate **15** did not undergo fragmentation under standard conditions[11] or at elevated temperatures. Although the geometry of **15** is not ideal for fragmentation,[12] it was not obvious that the deviation accounted for this failure. Nevertheless, we examined olefinic analog **17**,[13] which appeared to have a slightly improved geometry for fragmentation.[14] Pleasingly, treatment of **18** under standard conditions gave the desired cyclononadienone **1**.

Further analysis provided several insights into the structure and reactivity of **1**. This substance is a low melting crystalline solid that is difficult to manipulate in crystalline form, and we have been unsuccessful in obtaining crystallographic data for this material.



Scheme 2. Reactions and conditions: (a) (i) Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$, 25 °C; (ii) CuLi(hexynyl)$_2$, acrolein, HMPA, TMSCl, −78 °C to −30 °C, 30%; (b) TBAF, AcOH, THF, 0 °C, 93%; (c) dicyclohexylboran, hexanes, diethylzinc, 0 °C.



Scheme 3. Reactions and conditions: (a) $NaBH_4$, methanol, 0 °C, 77%; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 82%; (c) $Li_{(s)}$, $NH_{3(l)}$, reflux, 47%; (d) TsCl, pyridine, DMAP, $CHCl_3$, 0 °C to rt, 70%; (e) KH, THF, rt to reflux; NaH, THF, rt to reflux; NaH, DMF, rt; NaH, DMSO, rt; (f) (i) MsCl, TEA, 0 °C; (ii) DBU neat, 80 °C, 53% (from **12**); (g) $Li_{(s)}$, $NH_{3(l)}$, reflux, 40%; (h) TsCl, pyridine, DMAP, $CHCl_3$, 0 °C to rt, 80%; (i) NaH, DMSO, rt, 60%.

The optical rotation [$\alpha_D = -17.0$] is in agreement with the earlier report. The highest directly observed enantiopurity of **1** was 87% ee. This was achieved by chiral HPLC analysis immediately upon extraction from the fragmentation reaction followed by filtration through a plug of silica gel. Alternatively, oxidative trapping of **1** with DMDO followed by flash column chromatography gave epoxide **19**[13] in 90% ee. Although a small degree of racemization takes place during HPLC analysis, this method was used to evaluate the stability of **1**. Much slower than *trans*-cyclononene, compound **1** racemizes with $t_{1/2} = 32$ h, 23 °C ($k_{rac} = 3.0 \times 10^{-6}$ s^{-1}, Table 1 and Fig. 1).

NMR analysis strongly suggests that the structure represented as **1** is the dominant conformer in solution.[15] Presumably, **1** racemizes by way of **con-1**, though we have not observed this or other related species. For example, variable temperature ^{1}H NMR analysis of **1** proved invariant from 25 °C to 55 °C. Consistent with these observations, computational analysis suggests that **1** is more stable than **con-1** by 4.2 kcal/mol.[16]

As indicated above, DMDO epoxidation gave **19** in high yield (96%). Indeed, dissymmetric ketone **1** participates in a number of stereoselective transformations. Our initial attempts focused on Diels–Alder reaction in the presence of cyclopentadiene, which did not react at room temperature. Lewis acids Me_2AlCl, Et_2AlCl,

Table 1
Racemization of **1**

Entry	Time (h)	ee[a,b] (%)
1	0	84.4
2	5.5	74.2
3	9.25	68.0
4	23	51.0
5	33.5	40.6

[a] Based on a reversible reaction model, $y = -\ln(ee\%)$.
[b] Racemization rate found: $k = 3.0 \times 10^{-6}$ s^{-1} (298 K).

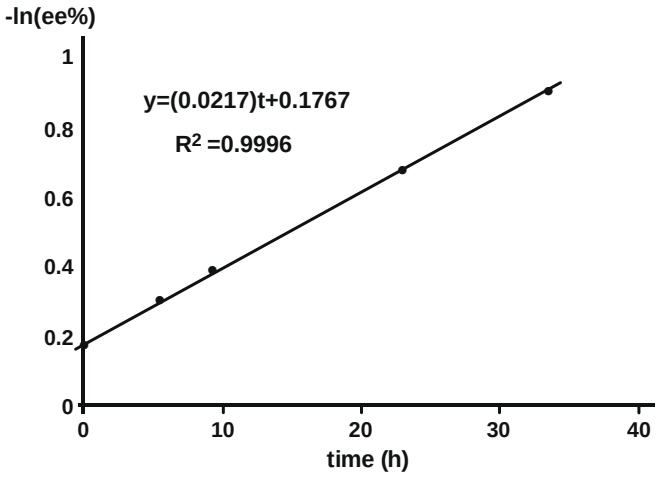
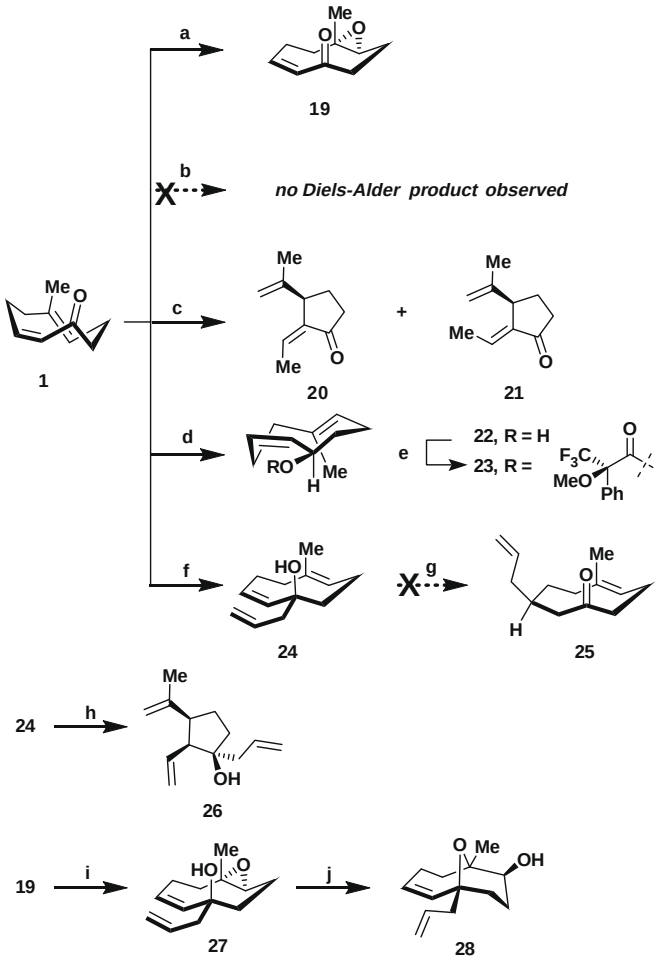


Figure 1. Plot of −ln(ee%) versus time.[17]

and $AlCl_3$ also failed to promote this reaction.[18] No cyclopentadiene cycloaddition product was observed at elevated temperatures. Instead, **20** and **21** were obtained.[19] These α,β-unsaturated ketones are derived from Cope rearrangement of **1** followed by isomerization. Stereoselective hydride reduction of **1** gave the corresponding alcohol **22**[13] as a crystalline solid with no deterioration in enantiomeric purity, according to Mosher ester analysis (**23**).[20] Allylation produced **24** (75%). Compound **24** failed to undergo anion-accelerated oxy-Cope rearrangement at low temperature, and at higher temperature, only the transannular Cope product, trisubstituted cyclopentene **26**, was obtained. To further demonstrate the versatility of **1**, and to evaluate a potential alternative oxy-Cope sequence, **1** was epoxidized and then allylated to give **27**. Upon subjection to anion-accelerated oxy-Cope conditions, the transannular epoxide-opened product **28** was cleanly obtained (90%). Transannular cyclization of **19** to **28** occurs slowly at low temperature. Indeed, when the allylation of **1** was run at 0 °C, **28** was obtained in good yield (76%)[21] (see Scheme 4).

These studies elaborate earlier findings on cyclononadienone **1**, including several stereoselective transformations and insight into the structure of this interesting class of synthetically useful intermediates. Importantly, **19–29** are derived from **1**, and are obtained in enantioenriched form. Many dissymmetric compounds related to **1** should be readily accessible.



Scheme 4. Reactions and conditions: (a) DMDO, $CHCl_3$, 0 °C, 96%; (b) cyclopentadiene, rt/Lewis acid (see text), toluene, −78 °C to rt; (c) cyclopentadiene, toluene, 130 °C, 60%, 2:1;[3] (d) $NaBH_4$, methanol, 0 °C, 93%; (e) (*R*)-Mosher's acid, DCU, DMAP, CH_2Cl_2, rt, 80%; (f) allylmagnesium chloride, THF, 0 °C to rt, 75%; (g) KH, 18-crown-6, THF, reflux; (h) toluene, 130 °C; (i) allylmagnesium chloride, THF, −78 °C, 75%; (j) KH, 18-crown-6, THF, −78 °C to rt, 90%.

Acknowledgment

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12. Molecular modeling suggests that **15** is highly constrained and that the (HO)CCCO(Ts) torsion angle is 139° (see Ref. 16).
13. This compound was characterized by single crystal X-ray diffraction. Crystallographic data for compound **17**, **19**, and **22** have been deposited with the Cambridge Crystallographic Data Center, Nos. CCDC 712607 (**17**), CCDC 712606 (**19**), and CCDC 712605 (**22**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
14. Molecular modeling suggests that **18** is more highly constrained than **15**, and the (HO)CCCO(Ts) torsion angle for **18** is better suited for fragmentation (165°) (see Ref. 16).
15. NOSY analysis shows the olefin protons as proximal, cf. 3c.
16. Calculations used (DFT-B3LYP 6-31G(d, p)). (a) All structures were fully optimized by analytical gradient methods using the GAUSSIAN 03 suites, (a) Frisch, M. J.; Trucks, G. W.; Schlege, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C., et al GAUSSIAN *03, Revision E.01*; Gaussian: Wallingford, CT, 2004; Density functional (DFT) calculations used the exchange potentials of: (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; the correlation functional of: (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
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387–395; c Although these Lewis acids failed, trityl perchlorate was effective at promoting conjugate addition to this enone (Ref. 3c).

19. Assignments of **20** and **21** were based on the enone proton signals (5.88 ppm for cis, **20**, and 6.72 ppm for trans, **21**) by analogy to: Taber, D. F.; Jiang, Q.; Chen, B.; Zhang, W.; Campbell, C. L. *J. Org. Chem.* **2002**, *67*, 4821–4827.
20. For example, reduction of **1** (in one instance enone of 60% ee was used) provided **22** from which **23** was prepared as a mixture of diastereomers (dr = 4:1, corresponding to 60% ee of **22**). Crystallographic structure determination of **22** revealed this material to be a disordered solid composed of both enantiomers (see Ref. 13).
21. *Preparation and characterization of* **19**, **24**, *and* **28**. (a) **19**: To cyclononadienone **1** (50 mg, 0.333 mmol) was added DMDO in chloroform (2.5 ml, 0.2 M, 0.5 mmol) at 0 °C. After 5 min, the reaction mixture was concentrated and purified by flash chromatography (20% EtOAc/hexanes) to give epoxide **19** (53 mg, 96%) as a white crystalline solid. IR ν_{max}(neat)/cm^{-1} 2936, 1690, 1625, 1453, 1177, 980, 747; δ_H (500 MHz, $CDCl_3$) 6.28 (1H, dd, *J* = 12.3, 1.3 Hz), 5.81 (1H, ddd, *J* = 12.2, 9.1, 7.6 Hz), 3.10 (1H, dd, *J* = 11.8, 2.3 Hz), 2.77 (1H, td, *J* = 11.5, 7.7 Hz), 2.77 (1H, td, *J* = 11.5, 7.7 Hz), 2.72–2.62 (2H, m), 2.40 (1H, ddd, *J* = 11.4, 7.5, 1.5 Hz), 2.28–2.20 (1H, m), 2.16–2.05 (2H, m), 1.65 (1H, qd, *J* = 11.7, 7.5 Hz), 1.20 (3H, s), 0.97 (1H, dd, *J* = 12.5, 11.8 Hz); δ_C (125 MHz, $CDCl_3$) 206.5, 136.8, 134.9, 61.1, 59.3, 37.4, 35.9, 24.3, 21.8, 17.0; *m*/*z* (ESIMS) found: 167 $(M+H)^+$; calcd: 167. HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow Rate = 1 mL/min, UV = 230 nm, t_R = 13.1 min and t_R = 27.9 min (major, 90% ee). (b) **24**: To a solution of cyclononadienone **1** (22 mg, 0.146 mmol) in THF (0.5 mL) at 0 °C was added allylmagnesium chloride (2.0 M, in THF, 0.11 ml, 0.22 mmol). After 1 h, the reaction was quenched with saturated NH_4Cl, extracted with ether (3 × 10 mL), the organic fractions were combined, dried over Na_2SO_4, filtered, concentrated, and then the residue was purified by flash chromatography (3% EtOAc/hexanes) to yield alcohol **24** (21 mg, 75% yield) as a colorless oil. IR ν_{max}(neat)/cm^{-1} 3562, 2924, 1725, 1638, 1448, 996, 915, 743; δ_H (500 MHz, $CDCl_3$) 5.83 (1H, dddd, *J* = 17.0, 10.2, 8.5, 6.1 Hz), 5.37 (1H, dd, *J* = 12.7, 1.2 Hz), 5.29–5.03 (4H, m), 2.43 (1H tdd, *J* = 12.6, 11.9, 6.3), 2.32 (1H, ddt, *J* = 13.6, 6.1, 1.3 Hz), 2.20, (1H, qdd, *J* = 5.5, 2.5, 1.3 Hz), 2.17–2.05 (4H, m), 1.93 (1H, ddd, *J* = 13.8, 11.9, 6.3 Hz), 1.85 (1H, ddd, *J* = 13.8, 6.3, 1.6 Hz), 1.74 (3H, t, *J* = 1.2 Hz), 1.56 (1H, br s), 1.58–1.51 (1H, dt, m); δ_C (125 MHz, $CDCl_3$) 139.9, 134.1, 131.5, 127.9, 125,4, 118.6, 76.4, 48.6, 44.0, 36.2, 27.1, 25.1 17.0; *m*/*z* (ESIMS) found: 175 $(M-OH)^+$; calcd: 175. (c) **28**: To a solution of epoxide **19** (20 mg, 0.133 mmol) in THF (0.5 mL) at 0 °C was added allylmagnesium chloride (2.0 M in THF, 90 μl, 0.18 mmol). The mixture was stirred at 0 °C for 1 h. The reaction was then quenched with saturated NH_4Cl, extracted with ether (3 × 10 mL), the organic fractions were combined, dried over Na_2SO_4, filtered, concentrated, and then the residue was purified by flash chromatography (25% EtOAc/hexanes) to yield bicyclic alcohol **28** (19 mg, 76% yield) as a white solid. IR ν_{max}(neat)/cm^{-1} 3424, 2932, 1639, 1440, 1078, 912; δ_H (500 MHz, $CDCl_3$) 5.95–5.80 (2H, m), 5.13–4.99 (3H, m), 3.35 (1H, br s), 2.61–2.51 (1H, m), 2.31–2.14 (3H, m), 1.93–1.66 (5H, m), 1.64–1.55 (1H, m), 1.32–1.25 (1H, m), 1.20 (3H, s); δ_C (125 MHz, $CDCl_3$) 134.4, 134.0, 130.3, 117.4, 78.2, 75.6, 70.0, 48.6, 38.8, 27.0, 26.5, 23.3, 21.1; *m*/*z* (ESIMS) found: 231 $(M+Na)^+$; calcd: 231.