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A Bioinspired Cyclization Sequence Enables the Asymmetric Total Synthesis of Dictyoxetane

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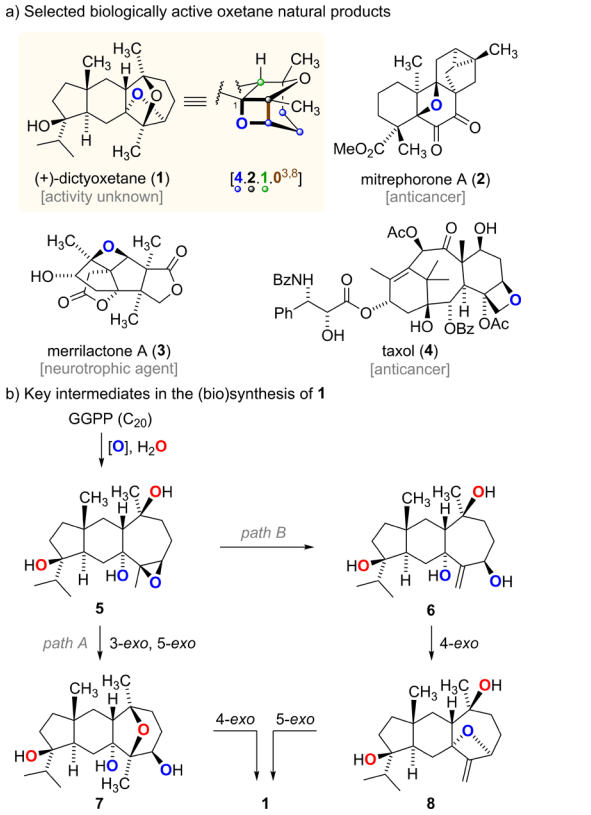
Supporting Information

ABSTRACT: We have developed the first synthesis of the unique oxetane containing diterpene (+)-dictyoxetane. Our retrosynthetic planning was guided by the putative biosynthesis of the unprecedented 2,7-dioxatricyclo-[4.2.1.0^{3,8}]nonane ring system. A bioinspired 4-*exo*-tet, 5-*exo*-trig cyclization sequence enabled the construction of the synthetically challenging dioxatricyclic framework. The overall synthesis proceeds in 15 linear steps from a known and readily available *trans*-hydrindane fragment. In addition, we were able to realize the first dyotropic rearrangement of an epoxide−oxetane substrate.

Natural products containing oxetanes often display strong and intriguing biological activities. However, their occurrence is very rare and less than a dozen have been reported to date (Scheme 1a).[1] Until the development of taxol (**4**) as a potent anticancer agent, medicinal chemistry has focused little study toward this unique structural motif. Oxetanes are highly polar heterocycles that have only recently been identified as efficient hydrogen bond acceptors and valuable surrogates for the *gem*-dimethyl group in drug discovery.[2] (+)-Dictyoxetane (**1**) was first isolated from the brown alga *Dictyota dichotoma* (Krusadai Island, India) in 1985 and contains an oxetane embedded in a synthetically challenging and unique 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane ring system.[3] As biological studies of **1** have not been reported yet and authentic material is currently unavailable,[4] several attempts were made to access the natural product in the chemical laboratory. Despite considerable efforts, only the syntheses of the more accessible *trans*-hydrindane framework[5] and simplified model systems of the dioxatricyclic substructure[6] have been accomplished so far. In seminal work by Hoffmann, promising antitumor activity of the dioxatricyclic subunit against HMO2 (human gastric carcinoma) and HEP G2 (human heptocellular carcinoma) cell lines was revealed, and a putative biosynthesis of **1** (Scheme 1b, path A) was proposed.[6a] It was hypothesized that the cyclization of geranylgeranyl pyrophosphate (GGPP) proceeds analogous to the dollabelane biosynthesis[7] and produces, after transannular cyclization to the 5−6−7 ring system and oxidation, epoxide **5**. A series of consecutive *exo*-tet cyclizations that involve tetrahydrofuran **7** as the key intermediate was suggested to lead to the formation of **1**. While studying the molecular model of **7**, we realized that formation of the strained annulated *trans*-tetrahydrofuran ring might be exceptionally challenging under nonenzymatic conditions.[8] Therefore, we envisioned that the formation of the isomeric allylic alcohol **6** could be a valuable

Scheme 1. Occurrence of Oxetane Natural Products and Bioinspired Synthetic Planning for Dictyoxetane (1)



alternative en route to **1** (Scheme 1b, path B). In this latter scenario, oxetane **8** is first formed via a 4-*exo*-tet cyclization. This ring closure involves a conformational change that places the methylene unit in close proximity to the tertiary alcohol at C10 and thus facilitates the final 5-*exo*-trig cyclization. Herein, we describe our efforts toward (+)-**1** and the first total synthesis of this unique natural product. In order to investigate the individual pathways of the biosynthetic proposals, we decided to directly target protected forms of compound **5** and its isomer **6**.

We first designed a synthetic route to the 5−6−7 ring fragment **14**, which features the full carbon skeleton of **1**, starting from Grainger's *trans*-hydrindane **10** (Scheme 2).[5] The latter can be readily prepared from 2-methylcyclopentenone (**9**), employing a very elegant phosphorane-mediated, pinacol-like rearrangement

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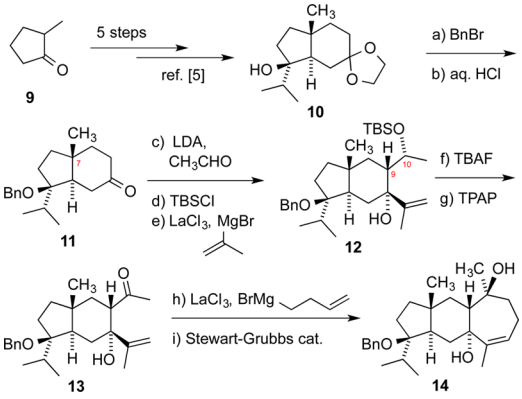
Scheme 2. Synthesis of the Full Carbon Skeleton of Dictyoxetane (1)[a]



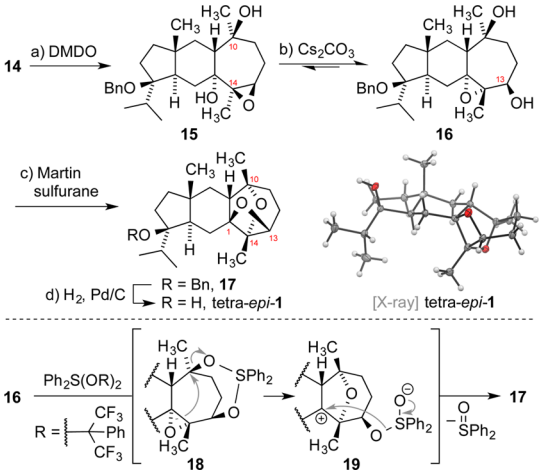
[a]Reagents and conditions: (a) BnBr, KHMDS, THF, −78 to 23 °C; (b) aq. 4 M HCl, THF, 23 °C, 85% over three steps; (c) LDA, CH_3CHO, −78 °C; (d) TBSCl, imidazole, DMAP, DMF, 23 °C, 80% over two steps, 10:1 d.r. at C10; (e) $LaCl_3$·2LiCl, isopropenylmagnesium bromide, THF, 0 °C, 93%; (f) TBAF, THF, 0 to 23 °C; (g) TPAP, NMO, 4 Å MS, CH_2Cl_2, 23 °C, 87% over two steps; (h) $LaCl_3$·2LiCl, 3-butenylmagnesium bromide, THF, 0 °C, 69%, 27% **13**; (i) Stewart−Grubbs cat. (25 mol %), 2,6-dichloro-1,4-benzoquinone, toluene, 111 °C, 55%, 25% recovered diene.

to establish the *trans*-ring junction. As outlined below, the sterically hindered tertiary alcohol of **10** was converted to the corresponding benzyl ether and hydrolysis of the ketal then gave access to multigram quantities (>6 g) of ketone **11**.

Next, a remarkably selective aldol reaction of the lithium enolate derived from **11** with acetaldehyde was carried out. Based on the stereodiscriminating effect of the quaternary center at C7, the aldol product was formed as a single diastereomer at C9 and as an inconsequential 10:1 mixture at C10. After protection of the β-hydroxy ketone as the corresponding silyl ether, the product was treated with isopropenylmagnesium bromide in the presence of the lanthanum(III) chloride bis(lithium chloride) complex[9] furnishing allylic alcohol **12** in high yield and excellent diastereoselectivity.[10] Conducting the analogous transformation in the absence of the lanthanide salt or without prior silyl ether formation proved to be significantly lower yielding and less diastereoselective. Subsequent removal of the silyl ether, followed by Ley−Griffith oxidation (TPAP, NMO),[11] then gave ketone **13** in 87% yield over two steps. Initial attempts to add 3-butenylmagnesium bromide to **13** proved unexpectedly challenging, and very low conversion of the starting material was observed, presumably due to facile enolization of this substrate. Fortunately, this problem could be addressed by premixing the β-hydroxyketone **13** again with lanthanum(III) chloride bis(lithium chloride) complex followed by addition of the Grignard reagent at 0 °C. This modification increased the conversion beyond 70% and provided the corresponding diene as a single diastereomer. To complete the synthesis of the 5−6−7 tricycle **14**, we then investigated the ring-closing metathesis of this diene substrate. After careful screening of the reaction parameters (catalyst, concentration, additives, temperature), the best result for formation of tricycle **14** was achieved using the Stewart−Grubbs catalyst[12] and 2,6-dichloro-1,4-benzoquinone as an additive.[13] The required high temperature (111 °C), high catalyst loading (25 mol %), and prolonged reaction time (40 h) are indicative of the challenge to form a seven-membered ring containing a trisubstituted olefin adjacent to a tertiary alcohol by means of ring-closing metathesis.[14]

Exposure of **14** to an excess of dimethyldioxirane (DMDO) cleanly gave epoxide **15** and traces of the product resulting from α-epoxidation (Scheme 3). With access to **15** we were poised to

Scheme 3. Synthesis of Tetra-*epi*-dictyoxetane (tetra-*epi*-1)[a]



[a]Reagents and conditions: (a) DMDO, acetone, CH_2Cl_2, −78 °C, ≥99%, ≥15:1 d.r.; (b) Cs_2CO_3, MeOH, 60 °C, 22% **15**, 59% **16**; (c) Martin sulfurane, CH_2Cl_2, 0 °C; (d) H_2, Pd/C, THF, 23 °C, 60% over two steps.

investigate the proposed, key *exo*-cyclization sequence to **1**. Numerous attempts to directly activate the epoxide with various acids and fuse the oxygen bridge between C10 and C14 were met with failure. While mild activation of **15** did not lead to any conversion, more forcing conditions (BF_3·OEt_2; $Yb(OTf)_3$; $HClO_4$; *p*-TsOH) led to complete decomposition of the starting material. Eventually, it was discovered that the postulated 3-*exo* rearrangement[6a] could be induced under basic conditions (Cs_2CO_3, MeOH, 60 °C), leading to an approximate 1:2.5 thermodynamic distribution of **15** and **16**, from which the latter could be easily separated by column chromatography on silica gel. At this point we determined that epoxide **16** was also reluctant to undergo further 5-*exo*-cyclization under a variety of acidic ($KHSO_4$; $Yb(OTf)_3$; aq. HCl; $Ti(Oi\text{-}Pr)_4$; $MgBr_2$·OEt_2), basic (NaH; aq. LiOH), and neutral (CF_3CH_2OH; H_2O[15]) reaction conditions.

These results confirmed our hypothesis that the seemingly simple intramolecular epoxide opening reaction to form the *trans*-tetrahydrofuran of **1** is indeed exceptionally challenging. By analyzing the X-ray structure from deprotected **16** (see Supporting Information for details) we learned that the seven-membered ring adopts a chairlike conformation. Since this places C10-OH in an equatorial position, an energetically unfavorable conformational change would be required to bring C10-OH into close proximity of C14. This result further corroborated our increasing skepticism that the desired 5-*exo*-tet cyclization of epoxide **16** might not be feasible using common activation methods. Finally, in an attempt to eliminate C13-OH in order to both change the ring geometry and generate a more reactive allylic epoxide, we observed a remarkable reaction sequence. Treatment of **16** with Martin sulfurane[16] led to rapid consumption of the starting material and furnished dioxatricycle **17** without detectable amounts of any olefinic byproducts. Hydrogenolysis of the benzyl ether gave 1,10,13,14-tetra-*epi*-

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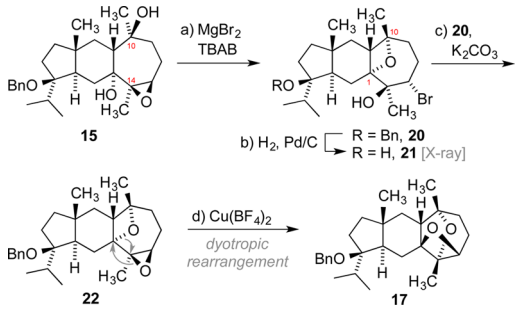
dictyoxetane (tetra-*epi*-**1**), whose structure was unambiguously confirmed by single-crystal X-ray analysis.

To rationalize this intriguing transformation, we compared and analyzed individual reaction intermediates of possible pathways, and the most likely proposed mechanistic scenario is illustrated in Scheme 3. We hypothesize that upon treatment of **16** with Martin sulfurane, the cyclic sulfurane **18** is formed. Driven by the strain release of epoxide opening and formation of a stabilized tertiary carbocation, **18** then rearranges to tetrahydrofuran **19**. Expulsion of diphenyl sulfoxide from **19** generates an alkoxide that immediately traps the carbocation to fuse the oxetane ring between C1 and C13 of dioxatricycle **17**. The direct generation of **17** from epoxide **15**, via in situ equilibration of **16**, can be excluded, as reaction of **15** with Martin sulfurane simply led to dehydration of C10-OH to give the *endo*-cyclic olefin. However, we initially also speculated that epoxide–oxetane **22** might be formed under the reaction conditions and could play a pivotal role during the rearrangement of **16** to dioxatricycle **17** (Scheme 4).

Scheme 4. Synthesis of Dioxatricycle 17 via Dyotropic Rearrangement[a]

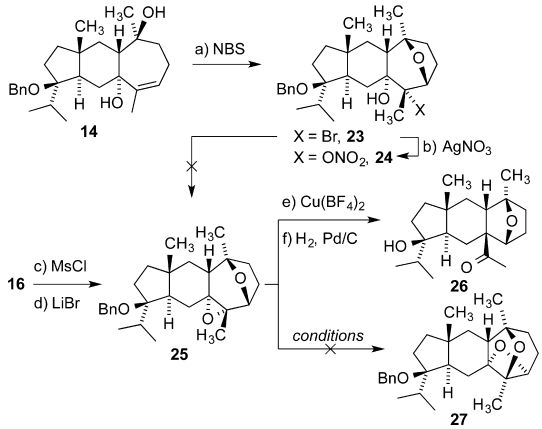


[a]Reagents and conditions: (a) $MgBr_2{\cdot}Et_2O$, TBAB, CH_2Cl_2, 23 °C, 51%; (b) H_2, Pd/C, THF, 23 °C, 83%; (c) **20**, K_2CO_3, MeOH, 0 °C, 94%; (d) $Cu(BF_4)_2{\cdot}xH_2O$, CH_2Cl_2, 23 °C, 36%.

In this context, we discovered that activation of **15** with magnesium bromide ethyl etherate in the presence of tetrabutylammonium bromide (TBAB) promoted smooth bromohydrin formation with concomitant oxetane ring closure between C1 and C10 to furnish **20**. Cleavage of the benzyl ether afforded diol **21** whose crystal structure confirmed the oxetane structural motif. Treatment of bromohydrin **20** with potassium carbonate in methanol provided the epoxide–oxetane **22** in 94% yield. At this stage, we found that **22** is left unreacted upon exposure to Martin sulfurane. Although this result further supported our mechanistic proposal and excluded any pathway based on transient formation of **22**, we were curious if a dyotropic rearrangement to dioxatricycle **17** could be induced by means of Lewis acid activation.[17] After careful experimentation, we discovered that treatment of epoxide–oxetane **22** with copper(II) tetrafluoroborate hydrate[18] promoted a strain-releasing dyotropic rearrangement to give the dioxatricycle **17** (36%) together with byproducts resulting from ring contraction (37%) and oxetane elimination (20%; see Supporting Information for details). To the best of our knowledge, this is the first example of a dyotropic rearrangement involving an epoxide–oxetane substrate.

In an attempt to apply a similar dyotropic rearrangement for the synthesis of **1**, we envisioned to extend this transformation to epoxide–tetrahydrofuran **25** (Scheme 5). Treatment of **14** with

Scheme 5. Attempted Dyotropic Rearrangement of 25[a]

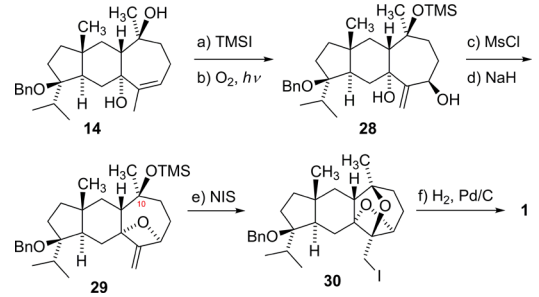


[a]Reagents and conditions: (a) NBS, CH_2Cl_2, 0 °C, ≥99%; (b) $AgNO_3$, $NaHCO_3$, acetone, 23 °C, 60%; (c) MsCl, NEt_3, CH_2Cl_2, −78 °C, 72%; (d) LiBr, Li_2CO_3, DMF, 70 °C, 80%; (e) $Cu(BF_4)_2{\cdot}xH_2O$, CH_2Cl_2, 40 °C; (f) H_2, Pd/C, THF, 23 °C, 90% over two steps.

active halogen sources such as *N*-bromosuccinimide (NBS) exclusively gave regioisomer **23**.[19] Activation of **23** with a panel of silver(I) sources ($AgNO_3$; $AgBF_4$; $AgNTf_2$) or under simple thermal conditions (CF_3CH_2OH, 2,6-lutidine) to promote the desired rearrangement to **27** via **25** was unsuccessful. Although we were able to abstract the tertiary bromide using silver(I) nitrate, exclusive formation of nitrate ester **24** occurred. Epoxide–tetrahydrofuran **25** could be finally prepared from **16** by mesylation and consecutive double S_N2 displacement. However, evaluation of several reaction conditions revealed that dyotropic rearrangement of **25** to **27** is not possible, owing to a competing semipinacol-type rearrangement generating the 5–6–6 tricyclic framework of **26**.[20]

After having failed to convert **15**, **16**, or **25** to the target compound, we returned to our alternative biosynthetic proposal, where we had envisioned constructing the dioxatricyclic substructure by forming the oxetane prior to the strained *trans*-tetrahydrofuran ring. It was found that photo-oxidation of the silyl ether derived from **14**, followed by reduction of the resulting hydroperoxide, gave allylic alcohol **28** as a single regio- and diastereomer in 71% yield (Scheme 6). While the subsequent 4-*exo*-tet cyclization of **28** could be achieved in a single transformation using *p*-toluenesulfonyl chloride and potassium

Scheme 6. Total Synthesis of (+)-Dictyoxetane (1) via Consecutive 4-*exo*-tet and 5-*exo*-trig Cyclizations[a]



[a]Reagents and conditions: (a) TMSI, CH_2Cl_2, 0 to 23 °C, 92%; (b) O_2, *hν*, TPP, DCE, 0 °C; PPh_3, 23 °C, 71%; (c) MsCl, NEt_3, CH_2Cl_2, −78 °C; (d) NaH, THF, 66 °C, 88% over two steps; (e) NIS, CH_2Cl_2, 23 °C; (f) H_2, Pd/C, THF, 23 °C, 80% over two steps.

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tert-butoxide, these conditions proved unreliable and gave irreproducible yields of oxetane **29**. Fortunately, a two-step procedure involving formation of the allylic mesylate and subsequent cyclization under basic conditions in refluxing tetrahydrofuran afforded oxetane **29** in consistently high yields. It was interesting to note that **29** showed severe signal broadening in the ^{1}H NMR spectrum at ambient temperature, indicating that formation of the oxetane had changed the conformation of the seven-membered ring in such a way that the C10-OTMS moiety had been brought into close proximity of the *exo*-methylene and could no longer freely rotate. Thus, exposure of **29** to *N*-iodosuccinimide (NIS) led to smooth cyclization with concomitant silyl ether deprotection, forming the *trans*-tetrahydrofuran of the dioxatricyclic substructure in **30**. The latter product was subjected to hydrogenolysis using palladium on carbon which induced simultaneous dehalogenation of the primary iodide and cleavage of the benzyl ether, furnishing (+)-dictyoxetane (**1**) whose spectroscopic data (^{1}H and ^{13}C NMR, HRMS, IR, $[\alpha]_D$) were in full agreement with those reported for the naturally occurring substance. Moreover, the positive $[\alpha]_D$ value of our synthetic sample established the absolute configuration of the natural product to be as depicted.

In summary, we have developed the first total synthesis of (+)-dictyoxetane (**1**) that contains a unique and synthetically challenging 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane ring system. A crucial modification of the proposed biosynthesis, specifically the use of sequential 4-*exo*-tet and 5-*exo*-trig cyclizations to form the respective oxetane and *trans*-tetrahydrofuran rings, enabled the construction of the complex dioxatricyclic framework. Moreover, we have discovered that epoxide−oxetanes are viable substrates for strain-releasing dyotropic rearrangements. Biological studies of **1** and tetra-*epi*-**1** are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03720.

Experimental details and spectroscopic data (PDF)
X-ray crystallographic data for tetra-*epi*-**1** and **21** (CIF)

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Notes

The authors declare no competing financial interest.

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(19) This result further supported our previous assumption that tetrahydrofuran ring formation between C10 and C14 is not directly possible.

(20) Cleavage of the benzyl ether after ring contraction facilitated purification.

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