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Chemoenzymatic Routes to Polyoxygenated Cyclooctenones Related to the Eastern Hemisphere of the Macrolactam Tripartilactam

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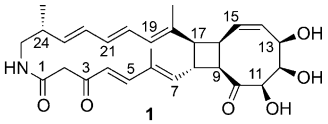
Abstract: Polyoxygenated cyclooctenones closely related to the enantiomeric form of the Eastern hemisphere of the structurally and biogenetically unusual macrolactam tripartilactam have been assembled from an enzymatically-derived and homochiral *cis*-1,2-dihydrocatechol. Key steps include the oxidative cleavage of the chlorinated double bond within a derivative of the starting *cis*-1,2-dihydrocatechol and a ring-closing metathesis reaction to establish the required eight-membered ring.

In 2012 Oh and co-workers reported the isolation of the tricyclic macrolactam tripartilactam (**1**) from a *Streptomyces* sp. found in the brood ball of the dung beetle *Copris tripartitus*.[1] The structure of this architecturally novel compound, which incorporates a cyclobutane fused, on its opposing faces, to both an 8- and an 18-membered ring, was established using a combination of spectroscopic techniques, most notably various 2D NMR spectroscopic methods. Mosher ester analyses were used to determine the absolute configuration of the stereogenic centers associated with the Eastern hemisphere while that of the remote methyl-bearing carbon C24 (located in the Western hemisphere) was identified through degradation and chemical correlation studies. Although the compound showed no significant antimicrobial or anticancer properties, it proved to be a moderate inhibitor of Na^+/K^+ ATPase (IC_{50} of 16.6 $\mu g\,mL^{-1}$). Intriguingly, it has been suggested[1] that the macrocyclic and polyunsaturated lactam **2**, a thus far undetected species in nature, engages in a transannular [2+2]-photocycloaddition reaction as the final step in the biogenesis of tripartilactam (**1**). Some support for such a proposal follows from earlier observations[2] that the structurally related macrolactam sceliphrolactam (**3**), of undefined stereochemistry at the associated sp^3-hybridized carbons, has been isolated from another insect-associated *Streptomyces* sp.



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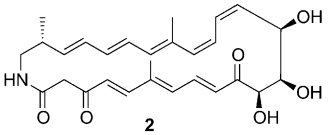

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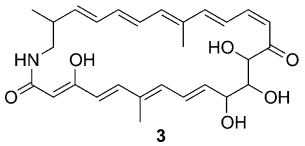

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The unique structural features and seemingly unusual biosynthetic origins of natural product **1** have prompted us to pursue its total synthesis. Two distinct approaches to the challenging[3] polyoxygenated cyclooctane substructure that represents the characteristic Eastern hemisphere of tripartilactam have now been explored and the outcomes of the relevant studies are reported herein. Each of these approaches exploited the enzymatically-derived and enantiomerically pure *cis*-1,2-dihydrocatechol **4**[4] as starting material and while the reaction sequences used ultimately lead to the optical antipodes of the relevant substructures, the availability of compound *ent*-**4**[5] means that the natural enantiomeric forms of these systems are accessible by exactly the same means.

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In the first approach it was envisaged that an intramolecular [2+2]-cycloaddition reaction between a terminal allene and a suitably tethered and carbonyl-conjugated alkene could deliver an adduct incorporating the target substructure[6] and wherein the associated cyclobutane ring had been assembled in near a biomimetic fashion, namely through formation of the C8–C17 and C9–C16 bonds (tripartilactam numbering). Syntheses of substrates suitable for testing this strategy are shown in Scheme 1 and began with the treatment of metabolite **4** with *N*-bromosuccinimide in aqueous THF. Conversion of the resulting bromotriol into the corresponding acetonide **5** (78% from **4**)[7] was achieved using 2,2-dimethoxypropane (2,2-DMP) in the presence of *p*-toluenesulfonic acid (*p*-TsOH). Reaction of compound **5** with

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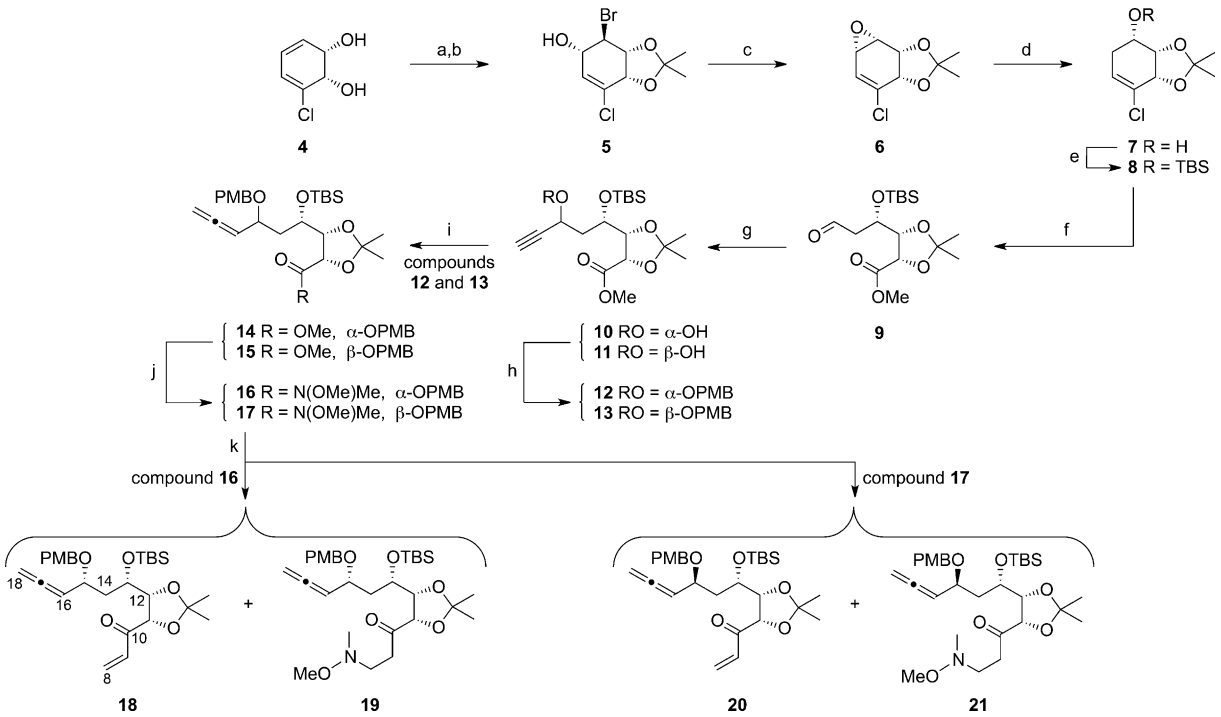
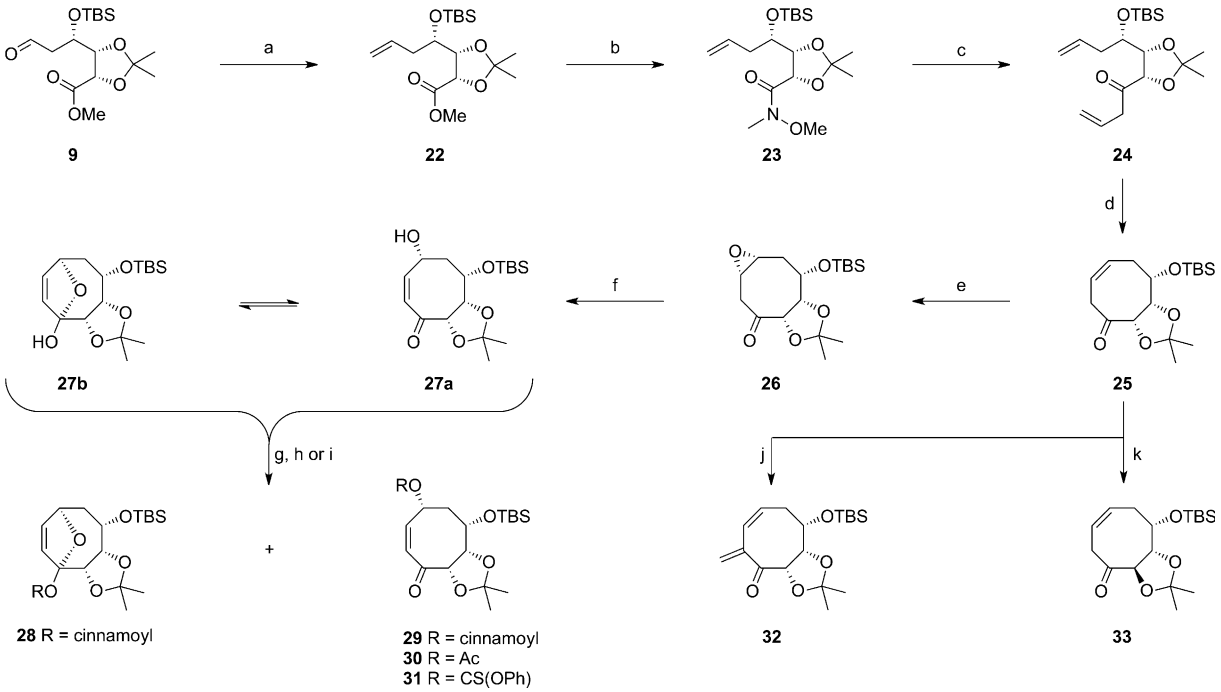


Scheme 1. Synthesis of the allenes **18** and **20**. a) NBS, 4:1 v/v THF/water, 0–18 °C, 4 h; b) 2,2-DMP, *p*-TsOH, 18 °C, 2 h, 78 %, 2 steps; c) NaH, THF, 0 °C, 1 h, 86 %; d) DIBAl-H, Et_2O, −78 to 0 °C, 2 h, 90 %; e) TBS-Cl, imidazole, DMF, 18 °C, 2 h, 98 %; f) O_3, pyridine, 4:1 v/v CH_2Cl_2/MeOH, −78 °C, 0.5 h then Ph_3P, 18 °C, 1 h, 86 %; g) ethynylmagnesium bromide, Et_2O, −78 to −15 °C, 1 h, 95 % of a ca. 1.4:1 mixture of **10** and **11**; h) 2-(4-methoxybenzyloxy)-4-methylquinoline, (+)-camphor-10-sulfonic acid (cat.), CH_2Cl_2, 40 °C, 16 h, 90 % (for **12**) and 83 % (for **13**); i) paraformaldehyde, CuI, *i*Pr_2NH, dioxane, 100 °C, 24 h, 78 % (for **14**) and 86 % (for **15**); j) HCl·HN(OMe)Me, *i*PrMgCl, THF, −15 °C, 1 h, 86 % (for **16**) and 77 % (for **17**); k) $H_2C{=}CHMgBr$, Et_2O, −78 °C, 1 h, 21 % (for **18**), 57 % (for **19**), 71 % (for **20**) and 14 % (for **21**).

sodium hydride in THF then afforded the previously reported epoxide **6** (86 %).[7] Regioselective reductive cleavage of compound **6** through hydride addition to the allylic carbon of the epoxide ring could be achieved using DIBAl-H, thus providing the crystalline homoallylic alcohol **7** (90 %).[8] Ozonolysis of the readily derived TBS-ether **8** (98 %) of compound **7** in the presence of methanol followed by reductive work-up using triphenylphosphine afforded the ω-oxoester **9**[8] (86 %) that reacted with ethynylmagnesium bromide at −78 °C to give a 1.4:1 mixture of the epimeric and chromatographically separable propargylic alcohols **10** and **11** (95 % combined yield). Independent treatment of each of these compounds with 2-(4-methoxybenzyloxy)-4-methylquinoline[9] in the presence of catalytic quantities of (+)-camphor-10-sulfonic acid then afforded the corresponding *p*-methoxybenzyl (PMB) ethers **12** (90 %) and **13** (83 %), respectively. Subjection of each of these products to the Searles–Crabbé allene-forming protocol[6b,10] using paraformaldehyde in the presence of cuprous iodide and diisopropylamine then gave the anticipated compounds **14** (78 %) and **15** (86 %), respectively. When treated with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of isopropylmagnesium bromide, the allenic esters **14** and **15** gave the corresponding and crystalline Weinreb amides **16** (86 %) and **17** (77 %), respectively.[8] Reaction of the former amide with vinylmagnesium bromide at −78 °C afforded the targeted enone **18** (21 %), but the major product of the reaction was the adduct of this with *N*,*O*-dimethylhydroxylamine, namely the β-aminoketone **19**, which was obtained in 57 % yield. When the epimeric amide **17** was reacted under the same conditions, but using a modified work-up, the desired vinyl ketone **20** (71 %) was obtained as the major product, although it was accompanied by the related aminoketone **21** (14 %).[11]

While compounds **18** and **20** bear some resemblance to the Eastern hemisphere of the putative biogenetic precursor **2** of tripartilactam (**1**), neither could be engaged in the hoped-for intramolecular [2+2]-cycloaddition reaction[6] so as to assemble bicyclo[6.2.0]decane substructures associated with the title natural product. Various reaction conditions were explored including those involving thermolysis, photolysis, and metal ions but all to no avail. Despite such outcomes, the reaction sequence defined above provides ready access to scaffolds strongly resembling the C8–C18 segment of compound **2** and in principle, therefore, is capable of being elaborated to this putative biogenetic precursor to tripartilactam (**1**). Of necessity, any such elaboration will require, among other things, the stereoselective elimination of the elements of PMBOH across the C14–C15 positions of these fragments.

In light of the lack of participation of compounds **18** and **20** in the desired [2+2]-cycloaddition process, alternate routes to polyoxygenated cyclooctanones resembling the Eastern hemisphere of the target natural product **1** were



Scheme 2. Synthesis of the cyclooctanes **25**–**33**. a) $Ph_3P=CH_2$, THF, 0 to 18 °C, 2 h, 76 %; b) HCl·HN(OMe)Me, *i*PrMgCl, THF, −15 °C, 1 h, 92 %; c) allylmagnesium bromide, THF, −78 °C, 1 h; d) Grubbs' II (cat.), CH_2Cl_2, 40 °C, 2 h, 78 %, 2 steps; e) DMDO, CH_2Cl_2, 0–18 °C, 16 h, 75 %; f) DBU, CH_2Cl_2, 18 °C, 6 h, 91 %; g) cinnamoyl chloride, DMAP, pyridine, CH_2Cl_2, 40 °C, 48 h, 19 % (for **28**) and 68 % (for **29**); h) Ac_2O, DMAP, pyridine, 40 °C, 24 h, 85 %, two steps; i) phenyl thionochloroformate, DMAP, pyridine, CH_2Cl_2, 40 °C, 48 h, 35 %, two steps; j) CH_2Cl_2, Et_3N, microwave irradiation, 100 °C, 4 h, 87 %; k) LiOH, 2:1 v/v MeOH/water, 18 °C, 2 h, 90 %.

pursued. An ultimately successful route to such motifs is shown in Scheme 2. This employs, as the pivotal step, a ring-closing metathesis (RCM) reaction[12] to assemble the required eight-membered ring, thus allowing for the possibility of introducing the four-membered ring associated with target **1** through a [2+2]-cycloaddition process that is complementary to the one pursued above (and proposed in the biogenetic conversion **2**→**1**). Specifically, then, the ω-oxo-ester **9** (readily obtained from compound **4** in six steps as shown Scheme 1) was subjected to a Wittig olefination reaction, and the resulting unsaturated ester **22** (76 %) was then converted into the corresponding Weinreb amide **23** (92 %) under standard conditions. Reaction of the latter compound with allylmagnesium bromide afforded the rather sensitive β,γ-unsaturated ketone **24**,[13] but under carefully controlled conditions **24** could be engaged in a RCM reaction when treated with Grubbs' second-generation catalyst,[14] thereby affording the expected cyclooctenone **25**[8] in 78 % yield (from **23**).[15] For the purposes of introducing additional functionality into the newly formed eight-membered ring, the alkene was treated with dimethyldioxirane (DMDO),[16] thus providing, in a completely stereoselective manner, the epoxide **26**[8] (75 %). Treatment of compound **26** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in a fully regiocontrolled cleavage of the epoxide ring and the formation of the γ-hydroxy-α,β-unsaturated-enone **27a** that exists almost exclusively (as judged by analysis of the derived spectral data) in the lactol form **27b** (91 %). Reaction of this material with cinnamoyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) gave a chromatographically separable mixture of acetal **28** (19 %) and enone **29**[8] (68 %) while analogous acetylation of compound **27** (using acetic anhydride and DMAP) only gave the corresponding enone **30**[8] (85 %). Similarly, treatment of compound **27** with phenyl thionochloroformate[17] afforded the anticipated thiocarbonate **31**, albeit in just 35 % yield (over the two steps from epoxide **26**). Two further and potentially significant reactions of the β,γ-unsaturated enone **25** were its ready methylenation, upon microwave irradiation in the presence of dichloromethane and triethylamine,[18] to give the dienone **32** (87 %) and its epimerization to the corresponding *trans*-ring-fused isomer **33**[8] (90 %) on exposure to LiOH in THF/water.

Efforts are now underway to elaborate compounds such as **25**–**32**, each of which embodies the polyoxygenated cyclooctane-containing Eastern hemisphere of *ent*-tripartilactam (*ent*-**1**), into more advanced precursors to this target. Results will be reported in due course.

Acknowledgements

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Keywords: *cis*-1,2-dihydrocatechol · cyclooctenone · enzyme catalysis · metathesis · tripartilactam

[1] S.-H. Park, K. Moon, H.-S. Bang, S.-H. Kim, D.-G. Kim, K.-B. Oh, J. Shin, D.-C. Oh, *Org. Lett.* **2012**, *14*, 1258.
[2] a) D.-C. Oh, M. Poulsen, C. R. Currie, J. Clardy, *Org. Lett.* **2011**, *13*, 752; b) M. Poulsen, D.-C. Oh, J. Clardy, C. R. Currie, *PLoS One* **2011**, *6*, e16763.
[3] For discussions on the significant challenges that apply to the synthesis of cyclooctane-containing systems and the solutions to some of these, see: a) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95; b) N. A. Petasis, M. A. Patane, *Tetrahedron* **1992**, *48*, 5757; c) G. Mehta, V. Singh, *Chem. Rev.* **1999**, *99*, 881; d) A. Michaut, J. Rodriguez, *Angew. Chem.* **2006**, *118*, 5870; *Angew. Chem. Int. Ed.* **2006**, *45*, 5740; e) Z.-X. Yu, Y. Wang, Y. Wang, *Chem. Asian J.* **2010**, *5*, 1072.
[4] For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: a) T. Hudlicky, D. Gonzalez, D. T. Gibson, *Aldrichimica Acta* **1999**, *32*, 35; b) M. G. Banwell, A. J. Edwards, G. J. Harfoot, K. A. Jolliffe, M. D. McLeod, K. J. McRae, S. G. Stewart, M. Vögtle, *Pure Appl. Chem.* **2003**, *75*, 223; c) R. A. Johnson, *Org. React.* **2004**, *63*, 117; d) T. Hudlicky, J. W. Reed, *Synlett* **2009**, 685; e) D. J.-Y. D. Bon, B. Lee, M. G. Banwell, I. A. Cade, *Chim. Oggi* **2012**, *30* (No. 5, Chiral Technologies Supplement), 22.
[5] a) D. R. Boyd, N. D. Sharma, S. A. Barr, H. Dalton, J. Chima, G. Whited, R. Seemayer, *J. Am. Chem. Soc.* **1994**, *116*, 1147; b) C. C. R. Allen, D. R. Boyd, H. Dalton, N. D. Sharma, I. Brannigan, N. A. Kerley, G. N. Sheldrake, S. C. Taylor, *J. Chem. Soc. Chem. Commun.* **1995**, 117.
[6] For relevant examples, see: a) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39*, 783; b) M. Himmelbauer, J.-B. Farcet, J. Gagnepain, J. Mulzer, *Org. Lett.* **2013**, *15*, 3098.
[7] M. G. Banwell, N. Haddad, T. Hudlicky, T. C. Nugent, M. F. Mackay, S. L. Richards, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1779.
[8] The structures of compounds **7**, **9**, **16**, **17**, **25**, **26**, **29**, **30**, and **33** were confirmed by single-crystal X-ray analysis. CCDC 956513 (**7**), CCDC 956514 (**9**), CCDC 956515 (**16**), CCDC 956516 (**17**), CCDC 956517 (**25**), CCDC 956518 (**26**), CCDC 956519 (**29**), CCDC 956520 (**30**), and CCDC 956521 (**33**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Selected data and ORTEPS are provided in the Supporting Information.
[9] a) E. O. Nwoye, G. B. Dudley, *Chem. Commun.* **2007**, 1436; b) C. A. Stewart, X. Peng, L. A. Paquette, *Synthesis* **2008**, 433.
[10] S. Searles, Y. Li, B. Nassim, M.-T. R. Lopes, P. T. Tran, P. Crabbé, *J. Chem. Soc. Perkin Trans. 1* **1984**, 747.
[11] The more favorable product distribution associated with the reaction leading to vinyl ketone **20** (as compared to that leading to congener **18**) derives from ensuring that an excess of aqueous ammonium chloride was used in the work-up and, therefore, that reduced quantities of the free base *N*,*O*-dimethylhydroxylamine were present.
[12] For a very useful and recent review article on the use of RCM reactions for the assembly of cyclooctenes see ref. [3d].
[13] Compound **24** was particularly prone to isomerization to the corresponding conjugated enone.
[14] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.
[15] A related cyclization leading to a polyoxygenated azacyclooctene has been described: J. D. White, P. Hrnciar, A. F. T. Yokochi, *J. Am. Chem. Soc.* **1998**, *120*, 7359.
[16] W. Adam, J. Bialas, L. Hadjiarapoglou, *Chem. Ber.* **1991**, *124*, 2377.
[17] M. J. Robins, J. S. Wilson, F. Hansske, *J. Am. Chem. Soc.* **1983**, *105*, 4059.
[18] Related methylenations have been observed using dibromomethane: Y.-S. Hon, T.-R. Hsu, C.-Y. Chen, Y.-H. Lin, F.-J. Chang, C.-H. Hsieh, P.-H. Szu, *Tetrahedron* **2003**, *59*, 1509.

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