Total Synthesis of (−)-Cylindrocyclophane A via a Double Horner-Emmons Macrocyclic Dimerization Event

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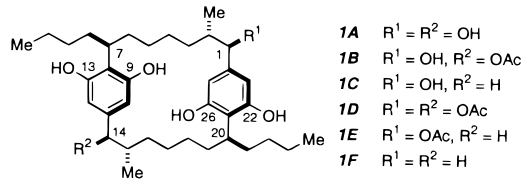
Cylindrocyclophanes A−F (**1**) are naturally occurring, cytotoxic [7.7]-paracyclophanes isolated by Moore and co-workers



Cylindrocyclophanes A-F

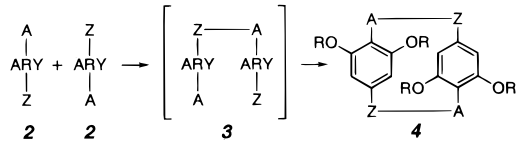
from the blue green alga, *Cylindrospermum licheniforme* Kützing (ATTC 29204).[1] The cylindrocyclophanes, along with the related nostocyclophanes A−D, are the only known natural [7,7]-paracyclophanes.[2] The first synthesis of a member of this family, cylindrocyclophane F (**1F**), was recently described by Smith and co-workers.[3] Here we report the synthesis of cylindrocyclophane A (**1A**), which includes two stereogenic and potentially reactive carbinol centers at the benzylic C(1) and C(14) positions.

We envisioned the construction of the C_2 symmetric macrocyclic core via head-to-tail dimerization of a bifunctional monomer **2** (Scheme 1). Macrocyclic dimerization by concurrent coupling[4] of both A−Z units to give **4** is inherently more efficient than stepwise coupling of differentially protected versions of **2** and subsequent macrocyclization of **3** following intervening deprotection.[3,4,5]

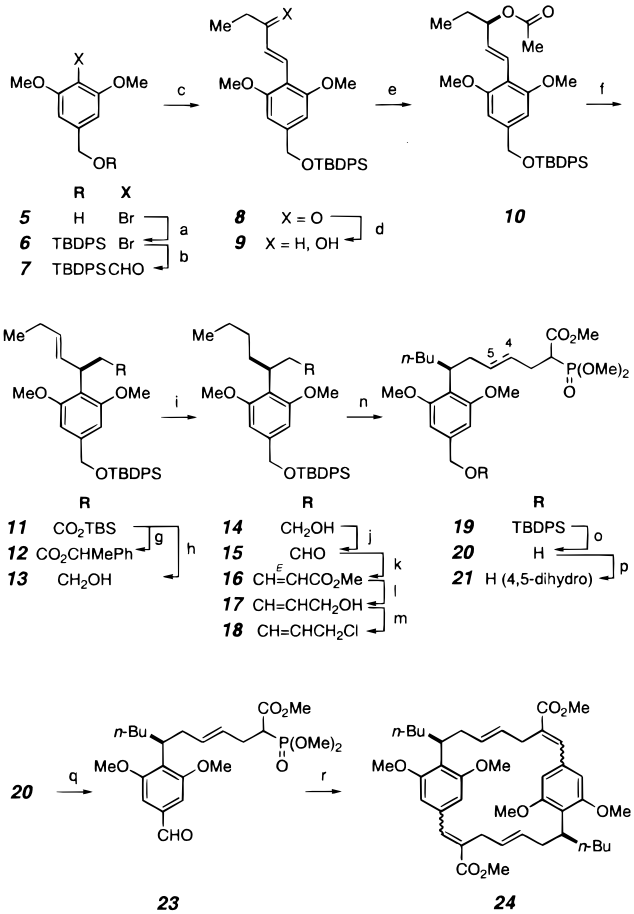
The synthesis proceeds in four steps (Scheme 2) from the known alcohol **(**5**)**[6] to the racemic allylic alcohol **9**. Kinetic resolution (Amano P-30 lipase, vinyl acetate, hexane) gave (*R*)-acetate **10** [99.4% ee (chiral HPLC)].[7] The recovered (*S*)-alcohol **9S** could be reoxidized to enone **8** and recycled.

The silylketene acetal derived from optically pure (*R*)-acetate **10** (KHMDS, −78 °C; TBSCl)[8] smoothly underwent [3,3]-sigmatropic rearrangement at room temperature to give TBS ester **11**. The ease of this rearrangement might originate with the lower

Scheme 1



Scheme 2[a]



[a] (a) TBDPSCl, Et_3N, CH_2Cl_2, 0 °C, 98%. (b) 2 equiv *t*-BuLi, Et_2O, −78 °C; DMF, −78 °C to rt, 92%. (c) $(MeO)_2P(O)CH_2COCH_2CH_3$, LiCl, DBU, CH_3CN, 70%. (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, 0 °C, 97%. (e) Amano P-30 lipase, hexanes, vinyl acetate, 4 Å MS, rt, 50% conversion, 94%. (f) KHMDS, THF, −78 °C; TBSCl, −78 °C to rt, 80%. (g) SiO_2, Et_2O, (*S*)-(−)-*sec*-phenethyl alcohol, DCC, DMAP, CH_2Cl_2 62%. (h) DIBAL, CH_2Cl_2, −78 °C, 95%. (i) H_2, Pd/C, EtOH, 99%. (j) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C; Et_3N, −60 °C to rt, 90%. (k) $(MeO)_2P(O)CH_2CO_2Me$, LiCl, DBU, CH_3CN, 80%. (l) DIBAL, CH_2Cl_2, −78 °C. (m) NCS, Me_2S, CH_2Cl_2, −30 °C, 89%. (n) $(MeO)_2P(O)CH_2CO_2Me$, *t*-BuOK, DMSO, 80%. (o) TBAF, THF, 0 °C, 94%. (p) H_2, Pt/C, EtOAc, 99%. (q) PDC, CH_2Cl_2, 94%. (r) LiCl, DBU, CH_3CN, 53%.

bond dissociation energy of the cinnamyl C−O bond. Chirality transfer during this rearrangement was very efficient (>99%).[9] Saturation of the alkene in **13** gave **14**, thereby establishing the requisite *n*-butyl group.

The primary alcohol **14** was transformed to phosphono ester **20** by an efficient six step sequence. This alkene was either hydrogenated to **21** (Pt/C[10] was used to avoid hydrogenolysis of

(1) (a) Moore, B. S.; Chen, J.-L.; Patterson, G. M. L.; Moore, R. E.; Brinen, L. S.; Kato, Y.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 4061. (b) Moore, B. S.; Chen, J.-L.; Patterson, G. M. L.; Moore, R. E. *Tetrahedron* **1992**, *48*, 3001. (c) Bobzin, S. C.; Moore, R. E. *Tetrahedron* **1993**, *49*, 7615.

(2) (a) Keehn, P. M.; Rosenfeld, S. M., Eds. *Cyclophanes*; Academic Press: New York, 1983. (b) Vogtle, F. *Cyclophane Chemistry*; Wiley: New York, 1993. (c) For a summary of naturally occurring phanes, see Chapter 11 in ref 2b.

(3) (a) Smith, A. B.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423. (b) A synthesis of cylindrocyclophane A from the Smith laboratory is described in the accompanying contribution.

(4) Hoye, T. R.; Ye, Z.; Yao, L. J.; North, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 12074.

(5) Successful relevant macrocyclic dimerization reactions were reported (a) Hoye, T. R.; Humpal, P. E. Presented at the 212th National Meeting of the American Chemical Society, Orlando, FL, August 1996; paper ORGN 173. (b) Humpal, P. E. Ph.D. Thesis, University of Minnesota, 1996.

(6) Nichols, D. E.; Dyer, D. C. *J. Med. Chem.* **1977**, *20*, 299.

(7) The absolute configuration of carbinol **9R** was inferred from that of the analogue lacking a substituent at the para position. The latter was deduced by ^{1}H NMR analysis of the corresponding Mosher esters. Mosher ester formation from **9** itself was complicated by both partial racemization and elimination, indicative of facile ionization to an allylic carbocation.

(8) (a) Rathke, M. W.; Sullivan, D. F. *Synth. Comm.* **1973**, *3*, 67. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(9) This was judged by ^{1}H NMR analysis of the *sec*-phenethyl ester **12** and confirmed at the stage of primary alcohol **13** by analysis of its Mosher ester. The absolute configuration of the new benzylic stereocenter was assumed to be *R* based upon a chair-transition state for the Claisen rearrangement.

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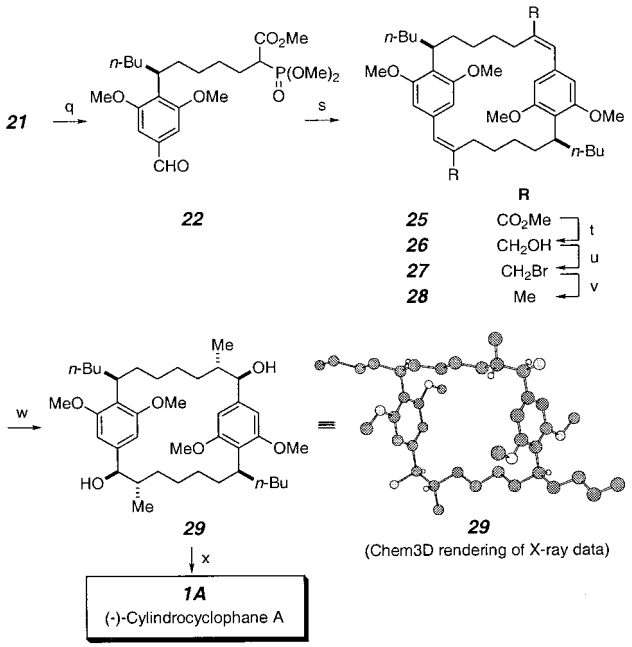
Scheme 3[a]



[a] (q) PDC, CH_2Cl_2, 96%. (s) NaH, benzene, cat. 15-crown-5, 55%. (t) DIBAL, CH_2Cl_2, 100%. (u) CBr_4, PPh_3, CH_2Cl_2. (v) LiBHEt$_3$, THF, rt, 91% overall from **26**. (w) IpcBH$_2$, THF, −20 °C to rt; H_2O_2, NaOH, 58%. (x) MeMgI, neat, 160 °C, 1 h, 60%.

the benzylic alcohol that was observed with Pd/C) and then oxidized (PDC) to the arylaldehyde **22** or directly oxidized (PDC) to the 4,5-dehydro aldehyde **23**. Each of the phosphonoester aldehydes **22** or **23** was a potential candidate to play the role of the bifunctional monomer **2**.

With monomer synthesis completed, we began macrocyclic dimerization studies. When aldehyde **23**, containing the *E*-4,5-alkene, was subjected to the Masamune olefination conditions (LiCl, DBU, CH_3CN, 0.01 M),[11] macrocyclic dienes **24** were obtained in 53% yield but as a mixture of ***EE*-24**, ***EZ*-24**, ***ZZ*-24** (∼2:4:1 ratio). Although the yield was acceptable, the enoate isomer distribution was unsatisfactory for further manipulations. When we examined the cyclization of the saturated phosphono ester aldehyde **22** under the same conditions, only a single stereoisomer, ***EE*-25**, was formed (Scheme 3); however, the yield was only 15%. This remarkable effect of the carbon chain structure on the stereoselectivity of the olefination reaction prompted us to screen various reaction conditions for the macrocyclization. Sodium hydride in benzene containing a catalytic amount of 15-crown-5 ether gave the most favorable results.[12] Macrocycle ***EE*-25** was formed in 55% yield and to the exclusion of the *Z,Z*-isomer, even when the reaction was scrutinized by in situ ^{1}H NMR monitoring in C_6D_6. The cyclization does not require high dilution; the yield does not suffer when the monomer concentration is raised from 0.001 to 0.02 M.

With access to ***EE*-25** secure, we addressed the introduction of the remaining four stereogenic centers and the completion of the synthesis of **1A**. The esters in ***EE*-25** were converted stereospecifically to the *E,E*-diene **28** (DIBAL-H reduction to **26**, CBr_4/PPh_3 [13] to bromide **27**, and Superhydride reduction to **28**[14]). Initial hydroboration/oxidation with $Me_2S{\cdot}BH_3$ gave a mixture of products, suggesting that the level of substrate control of the crucial hydroboration event was low. We turned to an asymmetric hydroboration of **28** using the hindered monoisopinocampheyl borane[15] derived from (+)-α-pinene. Following H_2O_2 oxidation the desired (*R,R*)-diol **29** was obtained in 58% yield, along with a small amount of the unsymmetrical (*R,S*)-diol (∼10−15%). The identity of **29** was first made by comparison with the reported ^{1}H NMR data for tetramethylcylindrocyclophane A (**29**), which Moore and co-workers had prepared by treatment of natural **1A** with diazomethane. This assignment was secured by a single-crystal X-ray structure determination.

All four methyl ethers in **29** were cleanly removed by fusion with excess methyl magnesium iodide at 160 °C[16] under vacuum to provide (−)-cylindrocyclophane A (**1A**) in ∼60% yield. No other byproducts were observed in this remarkable demethylation reaction in which both secondary benzylic alcohols were maintained. The structure of **1A** was confirmed by its melting point (276−278 °C; lit. 276−278 °C[1b]), optical rotation ($[\alpha]^{RT}_D = -20°$; lit. $[\alpha]^{RT}_D = -20°$ [1b]), HRMS (FAB), and ^{1}H NMR (in CD_3OD and in DMSO-d_6 [1b]) data.

In conclusion the synthesis of (−)-cylindrocyclophane A (**1A**) was achieved by the use of an efficient double Horner-Emmons macrocylic dimerization reaction. It is interesting that this process did not require high dilution and that it was more stereoselective when the less rigid saturated monomer **22** was used instead of the olefinic analogue **23**. The clean perdemethylation of the tetra-*O*-methyl ether **29** by the action of MeMgI at 160 °C warrants the use of these improbable, yet trivially implemented, conditions for the demethylation of many anisole derivatives.[17]

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Supporting Information Available: Experimental procedures for preparation of and characterization data for all new compounds and X-ray structural information for compound **29** are included as Supporting Information (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) To probe whether the enoates comprising the mixture of **24** were likely to be isomerizing under the reaction conditions, we performed the following pair of control experiments. Diene-dienoate ***ZZ*-24** was exposed at rt to 3,5-$(MeO)_2PhCHO$ and $MeO_2CCH_2PO(OMe)_2$ in the presence either of (i) NaH and 15-C-5 in C_6D_6 or of (ii) DBU and LiCl in D3CC≡N. The intermolecular olefination proceeded smoothly, but there was no observable change in the isomeric integrity of ***ZZ*-24**, even after each mixture was incubated for 27 h. It is therefore unlikely that the diene-dienoates **24** (or, we presume, **25**) are equilibrating under either of these sets of Horner-Emmons olefination conditions. The mixture of dienoate isomers appears result from a kinetically rather than thermodynamically controlled event.
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(14) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 849. (b) Nonacidic workup was required at this step to avoid isomerization of the alkenes.
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(16) (a) Mechoulam, R.; Gaoni, Y. *J. Am. Chem. Soc.* **1965**, *87*, 3273, wherein reference is made to the earlier unpublished use and recommendation of this method for cleavage of dimethyl resorcinols by Professor G. Ourisson. (b) Meerwein, H. *Houben-Weyl, Methoden der Organische Chemie*; Müller, E., Ed.; George Thieme Verlag: Stuttgart, 1964; Vol. VI, pp 160−164.
(17) For example, demethylation of sensitive ArOMe-containing intermediates in recent vancomycin syntheses was solved by the use of $AlBr_3$/EtSH, conditions that were not successful in the case of conversion of **29** to **1A**.