Total Synthesis of (±)-Punctaporonin B

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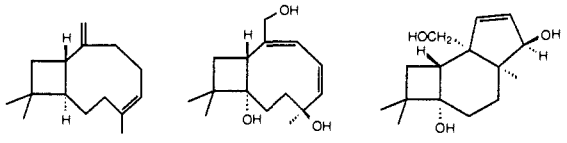
Received May 12, 1988

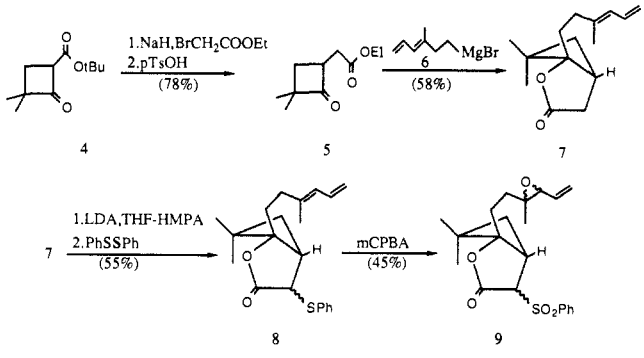
Since the landmark total synthesis of the hydrocarbon (±)-caryophyllene (**1**) by Corey in 1963, this rare series of bicarbocyclic



1 2 3

sesquiterpenes has received scant attention from the synthetic chemist.[1] This hiatus has been challenged in recent years by the structure elucidation of such intriguing 9-4 bicyclic terpenes as the 12-hydroxycaryophyllene-4,5-oxide,[2] the diterpene acetylcoriacenone,[3] and in 1984, by the still more highly functionalized diene triol, punctaporonin B (**2**).[4] Triol **2**, isolated from extracts of the drug fungus *Poronia punctata* (Linnaeus ex Fries) is a congener of several tricarbocyclic sesquiterpenes of which (-)-punctaporonin A (**3**)[5] has been very recently synthesized by Paquette and Sugimura.[6]

We describe the first total synthesis of racemic punctaporonin B by an efficient and potentially general strategy for the construction of such fused 9-4 systems. Our starting material was the known and readily accessible[7] cyclobutanone ester **4**, which

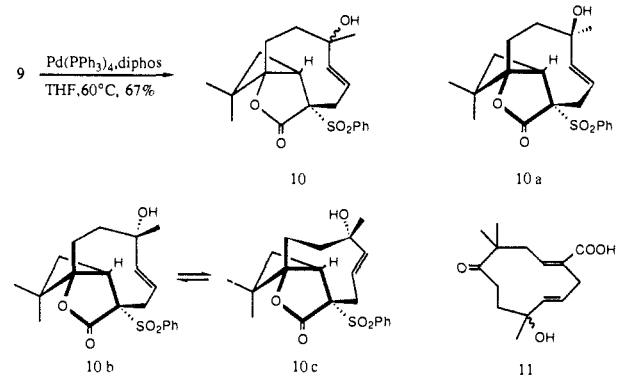


4 5 7

8 9

underwent C-alkylation (1.2 equiv of NaH, 1.2 equiv of $BrCH_2CO_2Et$, DMSO, room temperature, 3 h) and subsequent decarbo-*tert*-butoxylation (catalyst pTSA, C_6H_6 reflux, 2 h) to give the γ-keto ester **5** in 78% overall yield. Addition of the Grignard reagent **6**[8] (1.0 equiv of RMgX, THF, room temperature, 16 h) occurred trans to the ester chain to yield on workup the γ-lactone **7**. Phenylsulfenylation (1.1 equiv of LDA, THF, 1.0 equiv of HMPA, -78 °C, then 2 equiv of Ph_2S_2, 0 °C, 1 h) produced thioethers **8**, which were directly oxidized (3 equiv of MCPBA, solid K_2CO_3, CH_2Cl_2, room temperature, 16 h) to yield the diastereomeric mixture of epoxy sulfones **9**; no epoxidation of the terminal methylene was observed.

Treatment of this diastereomeric mixture with 10 mol% of $Pd(PPh_3)_4$ and 20 mol% diphos in THF at 60 °C for 1 h led with dramatic regioselectivity to a mixture of the (*E*)-cyclononene alcohol epimers **10** in 67% isolated yield. In contrast to the related



10 10a

10b 10c 11

closures described by Trost and Verhoeven[9] no trace of the regioisomeric cycloheptene products could be discerned by high field proton NMR, and none of the (*Z*)-cyclononene stereoisomer was detected. Product **10** could be readily separated by silica gel into a 1:2 ratio of fractions corresponding to the two carbinol epimers. The minor fraction, mp 202-203 °C, was shown by single-crystal X-ray analysis[10] to have the structure **10a**, corresponding to the non-natural series. The major fraction, presumably the carbinol epimer of **10a**, unexpectedly appeared to be a mixture of two similar compounds by 300 MHz ^1H NMR. This discrepancy was resolved by high-temperature ^1H NMR studies which showed the existence of slowly equilibrating cyclononene conformers (**10b** ⇌ **10c**) and by careful crystallization from MeCN to give a single conformer, mp 184-185 °C, for which X-ray crystallography established the structure in the crystal as conformation **10c**.[10]

With the identity of the major sulfone fraction thus established as the conformational isomer mixture **10bc** containing the full carbon skeleton of the target molecule, we explored the generation of the second double bond by elimination of $PhSO_2H$. Our direct attempts to generate a cyclononadiene system using DBU (DMSO, 60 °C, 16 h) or KO*t*-Bu (DMSO, room temperature)[11] failed, presumably because of the strain imposed by developing a bridgehead double bond within this rigid bicyclic framework. Vigorous treatment of the mixture **10** with KOMe in MeOH at reflux for 2 h led to diene *keto* acids having IR, MS, ^1H NMR, and ^{13}C NMR properties consistent with the Grob fragmentation product, cycloundecadienones **11**.

To alleviate the strain of the requisite diene, the lactone ring was opened as follows. Sodium amalgam reduction[9b] of **10bc** gave lactone **12**, which was resulfenylated (2.2 equiv of LDA, THF, -70 °C, then 2.0 equiv of $PhSSO_2Ph$, -50 °C, 1 h) to thioether **13**. Reduction of **13** (6 equiv of $LiAlH_4$, THF, room temperature, 20 min) followed by acetylation (excess Ac_2O-py, $CHCl_3$, 8 h, reflux) gave in 51% overall yield the triol monoacetate **14**. Oxidation, followed by sulfoxide elimination (5 equiv of $NaIO_4$, aqueous dioxane, catalyst HOAc, 35 °C, 16 h, then 80 °C in toluene, 30 min) gave an 80% yield of the (*E*,*E*)-diene monoacetate, which was deacetylated (KOMe, MeOH, room tem-

(1) (a) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1963**, *85*, 362; **1964**, *86*, 485. (b) Bertrand, M.; Gras, J.-L. *Tetrahedron* **1974**, *30*, 793.

(2) Wlodzimierz, M. D.; Grieco, P. A.; Huffman, J. C.; Rymkiewicz, A.; Wawrzun, A. *Phytochemistry* **1981**, *20*, 2733.

(3) Ishitsuka, M.; Kusumi, T.; Kakisawa, H.; Kawakami, Y.; Nagai, Y.; Sato, T. *J. Org. Chem.* **1983**, *48*, 1937.

(4) Anderson, J. R.; Edwards, R. L.; Freer, A. A.; Mabelis, R. P.; Poyser, J. P.; Spencer, H.; Whalley, A. J. S. *J. Chem. Soc., Chem. Commun.* **1984**, 917. The original designation of this group of punctatins has been superseded by the punctaporonins (Poyser, J. P., personal communication).

(5) (a) Anderson, J. R.; Briant, C. E.; Edwards, R. L.; Mabelis, R. P.; Poyser, J. P.; Spencer, H.; Whalley, A. J. S. *J. Chem. Soc., Chem. Commun.* **1984**, 405. (b) Poyser, J. P.; Edwards, R. L.; Anderson, J. R.; Hursthouse, M. B.; Walker, N. P. C.; Sheldrick, G. M.; Whalley, A. J. S. *J. Antibiot.* **1986**, *39*, 167.

(6) Paquette, L. A.; Sugimura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3841; **1987**, *109*, 3017.

(7) Agosta, W. C.; Herron, D. K. *J. Org. Chem.* **1969**, *34*, 2782.

(8) Howden, M. E.; Maercker, A.; Burdan, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1732.

(9) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 1597. (b) Trost, B. M.; Verhoeven, T. R. *Ibid.* **1980**, *102*, 4743. See, also: (c) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (d) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.

(10) Details of the X-ray single crystal structure will be given in our full paper. We thank Professor W. D. Jones for his guidance in the X-ray analysis.

(11) Hofmann, J. E.; Wallace, T. J.; Schriesheim, A. *J. Am. Chem. Soc.* **1964**, *86*, 1561. Manchand, P. S.; Rosenberger, M.; Saucy, G.; Wehrli, P. A.; Wong, H.; Chambers, L.; Ferro, M. P.; Jackson, W. *Helv. Chim. Acta* **1976**, *59*, 387.

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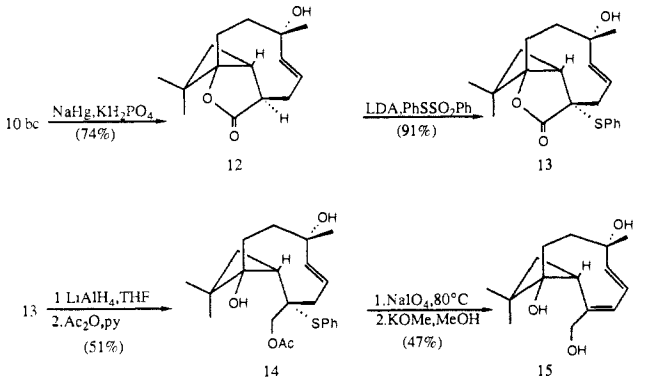

perature, 20 min, 58%) to the crystalline (*E*,*E*)-diene triol **15**, mp 112–114 °C.

The UV maximum of triol **15** (λ_{max} 237 nm, MeOH) and its 300 MHz ^{1}H NMR differed appreciably from those of the target molecule. However, when a dilute solution of **15** in CD_3OD was irradiated for 1 h by using a low-pressure UV source,[12] the isomerization monitored by NMR, chromatography, and recrystallization from EtOAc gave ca. 60% of colorless racemic punctaporonin B (**2**), mp 154–155 °C. The 300 MHz ^{1}H NMR spectra in both $CDCl_3$ and pyridine-d_5, the mass spectrum, the UV spectrum (λ_{max} 209 nm, MeOH, ϵ 6100), and the TLC behavior of this material were absolutely identical with the corresponding properties of natural punctaporonin B kindly supplied by Dr. J. P. Poyser (ICI Pharmaceuticals Division). Thus the first synthesis of (±)-**2** has been achieved in 13 steps from cyclobutanone **4**.[13]

Supplementary Material Available: Spectral data for **2**, **5**, **7**, **8**, **11**, **12**, **13**, and **15** (2 pages). Ordering information is given on any current masthead page.

(12) Cf. Shumate, K.; Fonken, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 1073.
(13) Partial support of this research by a Fulbright Award (to I.K.) and by Grant CA-18846 from the National Cancer Institute, NIH, USPHS, is gratefully acknowledged.

The Peptide Way to Macrocyclic Bifunctional Chelating Agents: Synthesis of 2-(*p*-Nitrobenzyl)-1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic Acid and Study of Its Yttrium(III) Complex

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Received March 21, 1988

Monoclonal antibody technology allows the specificity of an antibody for its antigen to be used in targeting cancer cells.[1] The conjugation of metals—particularly radionuclides such as ^{90}Y or ^{67}Cu—to monoclonal antibodies results in agents for radioimmunotherapy and other medical applications.[2-4] Chelators that

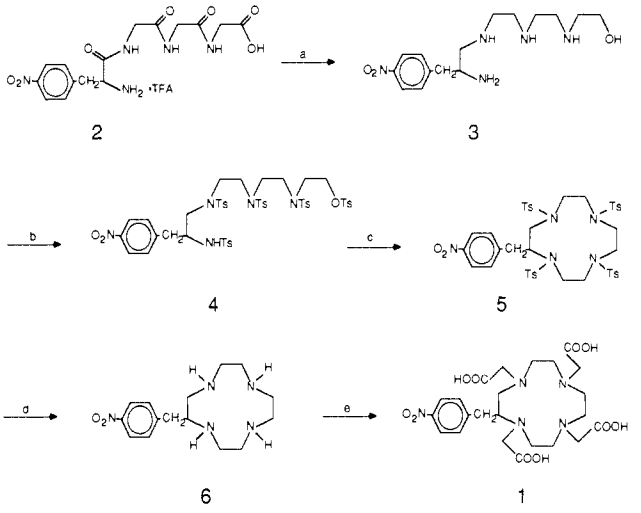

Figure 1. Synthesis of 2-(*p*-nitrobenzyl)-1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid, **1**. Tetrapeptide [L]-NO_2Phe-Gly-Gly-Gly (**2**) was prepared by standard methods.[11] (a) Reflux with 17 equiv of BH_3·THF, 31 h; 65% yield after silica gel chromatography. (b) Toluenesulfonyl chloride (5 equiv) in CH_3CN/Et_3N, 8 h, room temperature; 49% yield after silica gel HPLC. (c) Cs_2CO_3 in DMF, 5 h, 60 °C; 79% yield after silica gel HPLC. (d) 96% H_2SO_4, 16 equiv of C_6H_5OH, 48 h, 100 °C; 91% yield after C_{18} HPLC. (e) $BrCH_2COO^-$ (5 equiv), 3 h, pH 10, 70 °C; 58% yield after C_{18} HPLC.

can hold radiometals with high stability under physiological conditions are essential to avoid excessive radiation damage to nontarget cells.[5,6]

Derivatives of polyazamacrocycles (bearing a C-substituted functional group for antibody attachment) can exhibit remarkable kinetic inertness; for example, the copper complex of the 14-membered 6-(*p*-nitrobenzyl)-1,4,8,11-tetraazacyclotetradecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (nitrobenzyl-TETA) is very stable in human serum under physiological conditions, and a conjugate of this complex with a monoclonal antibody has tested well in tumor-bearing mice.[3b,7] Also, the gadolinium complex of the 12-membered 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (DOTA) is a stable, useful contrast agent for magnetic resonance imaging.[8] Desreux and co-workers[9] have shown that complexes of lanthanides with DOTA have formation constants that are several orders of magnitude higher than TETA; thus the 12-membered macrocycle is the favored target for binding trivalent yttrium.

Macrocyclic polyamines, the key precursors to macrocyclic bifunctional chelating agents, are synthesized by bimolecular cyclizations.[10] Competition between polymerization and the

(1) DeNardo, S. J.; Peng, J. S.; Denardo, G. L.; Mills, S. L.; Epstein, A. L. *Nucl. Med. Biol.* **1986**, *13*, 303.
(2) DeNardo, S. J.; Jungerman, J. A.; DeNardo, G. L.; Lagunas-Solar, M. C.; Cole, W. C.; Meares, C. F. In *The Developing Role of Short-Lived Radionuclides in Nuclear Medical Practice*; Paras, P., Theissen, J. W., Eds.; US Department of Energy: Washington, DC, 1984.
(3) (a) Order, S. E.; Klein, J. L.; Leichner, P. K.; Frinke, J.; Lollo, C.; Carlo, D. J. *Int. J. Radiation Oncology Biol. Phys.* **1986**, *12*, 277. (b) Deshpande, S. V.; DeNardo, S. J.; Meares, C. F.; McCall, M. J.; Adams, G. P.; Moi, M. K.; DeNardo, G. L. *J. Nucl. Med.* **1988**, *29*, 217.
(4) (a) Halpern, S. E.; Hagan, P. L.; Garver, P. R.; Kozol, J. A.; Chen, A. W. N.; Frincke, J. M.; Bartholomew, R. M.; David, G. S.; Adams, T. H. *Cancer Res.* **1983**, *43*, 5347. (b) Hnatowich, D. J.; Layne, R. L.; Lanteigne, D.; Davis, M. A.; Griffin, T. W.; Doherty, P. W. *Science (Washington, D.C.)* **1983**, *220*, 613. (c) Pimm, M. V.; Perkins, A. C.; Baldwin, R. W. *Eur. J. Nucl. Med.* **1985**, *11*, 300.
(5) Klein, J. L.; Leichner, P. K.; Callahan, K. M.; Kopher, K. A.; Order, S. E. *Antibody, Immunoconjugates, and Radiopharmaceuticals* **1988**, *1*, 55.
(6) Meares, C. F.; Wensel, T. G. *Acc. Chem. Res.* **1984**, *17*, 202.
(7) (a) Moi, M. K.; Meares, C. F.; McCall, M. J.; Cole, W. C.; DeNardo, S. J. *Anal. Biochem.* **1985**, *148*, 249. (b) Moi, M. K.; Yanuck, M.; Deshpande, S. V.; Hope, H.; DeNardo, S. J.; Meares, C. F. *Inorg. Chem.* **1987**, *26*, 3458.
(8) (a) Margerstadt, M.; Gansow, O. A.; Brechbiel, M. W.; Colcher, D.; Baltzer, L.; Knop, R. H.; Girton, M. E.; Naegele, M. *Magn. Reson. Med.* **1986**, *3*, 808. (b) Runge, V. M.; Jacobson, S.; Wood, M. L.; Kaufman, D.; Adelman, L. S. *Radiology* **1988**, *166*, 835. (c) Bousquet, J. C.; Saini, S.; Stark, D. D.; Hahn, P. F.; Nigam, M.; Wittenberg, J.; Ferrucci, J. T. *Radiology* **1988**, *166*, 693.
(9) Loncin, M. F.; Desreux, J. F.; Merciny, E. *Inorg. Chem.* **1986**, *25*, 2646.

0002-7863/88/1510-6266$01.50/0