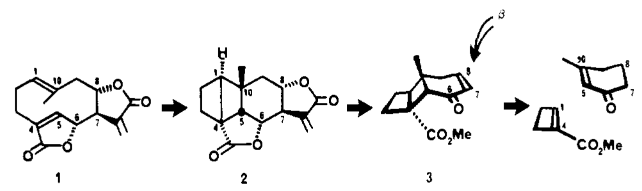
Total Synthesis of (±)-Isabelin[1]

Sir:

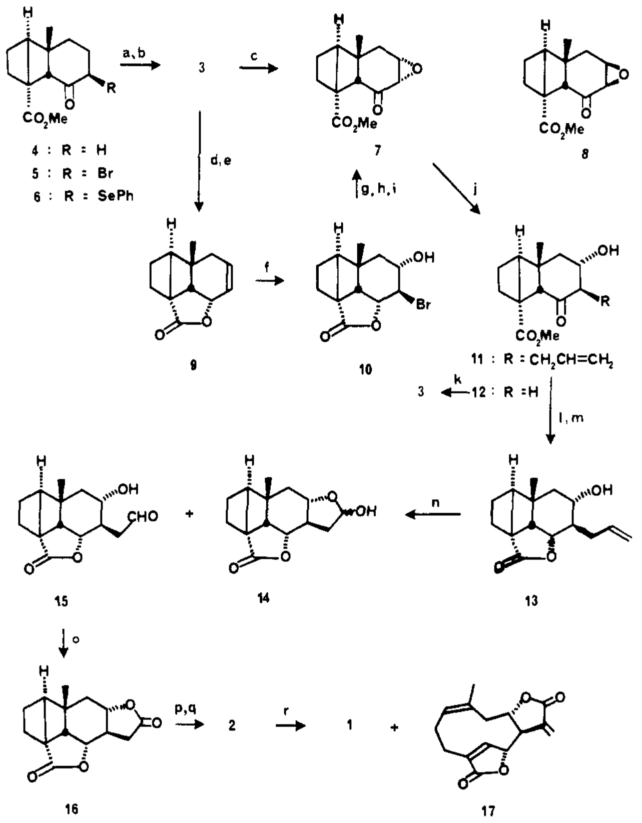
Since the pioneering studies of Ruzicka and co-workers,[2] many-membered ring chemistry has grown to encompass a wide range of natural[3] and nonnatural[4] compounds whose properties and activities have attracted a multidisciplinary interest. The germacrane sesquiterpenes have figured prominently in this development, initially because of their pivotal role as both biogenetic and synthetic precursors to a variety of sesquiterpene families[3a] and more recently due to the wide spectrum of biological activities exhibited by certain members of this class.[5] To date, however, efforts culminating in germacrane total synthesis have been relatively few in number.[6] To some extent, this finding reflects the substantial difficulties encountered in the synthesis of medium-ring carbocycles and heterocycles in general and, in particular, the formidable problems associated with setting stereochemistry on such chemically labile and frequently conformationally mobile networks.

This communication describes a short, stereocontrolled synthesis of the germacranolide dilactone (±)-isabelin (1)[8] in a fashion which indicates that this initial entry into the α-C-6, α-C-8 dioxygermacranes could be easily extended to encompass all of the known C-6, C-7, and C-8 stereorelationships.[9] The synthesis design (Scheme I) draws on our previous studies on a photothermal olefin metathesis concept for medium-ring synthesis[10] and, in this instance, exploits the convex topography of the tricyclo[$4.4.0.0^{2,5}$]decane intermediates and the C-1, C-10/C-4, C-5 double-bond protection provided by the cyclobutane subunit in order to control and facilitate appendage introduction and elaboration.

Scheme I



Scheme II



[a] (a) LiN(i-Pr)$_2$, THF, −78 °C; Me$_3$SiCl; (b) Pd(OAc)$_2$, CH$_3$CN, 22 °C, 24 h; (c) Cl$_2$, H$_2$O; K$_2$CO$_3$, CH$_3$COCH$_3$; (d) NaBH$_4$ (1 equiv), CeCl$_3$·xH$_2$O (1 equiv), MeOH, 0 °C, 10 min then 1 N HCl; (e) p-TsOH·H$_2$O, C$_6$H$_6$, 22 °C, 15 min; (f) NBS, DME/H$_2$O (3:2), 22 °C, 8 h; (g) K$_2$CO$_3$, CH$_3$COCH$_3$, 22 °C, 24 h; 0.1 N NaOH, 22 °C, 12 h; (h) RuO$_2$·H$_2$O (catalyst), NaIO$_4$; (i) CH$_2$N$_2$, Et$_2$O/H$_2$O (3:1); (j) (CH$_3$)$_2$CuLi (2.4 equiv), HMPA (5 equiv), Et$_2$O, −25 °C; CH$_2$=CHCH$_2$I (20 equiv), HMPA, −20 °C; NH$_4$Cl; (k) p-TsOH, C$_6$H$_6$; (l) NaBH$_4$, MeOH, −10 °C, 0.5 h; (m) 1 N HCl, 22 °C, 1 h; (n) O$_3$, MeOH/H$_2$O (20:1), NaOAc, −78 °C; Me$_2$S, 22 °C, 1.5 h; (o) Ag$_2$CO$_3$/Celite, C$_6$H$_6$, 80 °C, 24 h; (p) LiN(i-Pr)$_2$, THF, −60 °C; CH$_2$N(CH$_3$)$_2$$^+I^-$; (q) MeI, THF/MeOH (2:1); Na$_2$CO$_3$, CH$_2$Cl$_2$, H$_2$O; (r) PhCH$_3$ solution, resealable tube, 200 °C, 40 min.

Enone 3 was viewed as a key germacrane precursor since its direct epoxidation was expected to provide the commonly en-

---

[1] (a) Taken in part from the Ph.D. Thesis of J.C.L., Harvard University, 1979. (b) Portions of this work were presented at the ACS/CSJ Chemical Congress, Honolulu, Hawaii, April 1-6, 1979; ORGN 115.

[2] A transcript of a lecture given by Ruzicka at University College, London on February 27, 1934 which summarized his early studies on many-membered rings can be found in *Chem. Ind.* **1935**, *54*, 2, and is accompanied by an editorial which also merits perusal. Cf. ref 3.

[3] Recent reviews include germacradienes: (a) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47. Cembranes: (b) Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A. *Ibid.* **1979**, *36*, 286. Macrolides: (c) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (d) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (e) Back, T. G. *Ibid.* **1977**, *33*, 3041. References on polyene macrolides, cytochalasans, *ansa* antibiotics, and related many-membered ring natural products are given in ref 3c-e.

[4] The following reviews are representative. Host-guest complexes: (a) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8. Cryptates: (b) Lehn, J.-M. *Ibid.* **1978**, *11*, 49. Macrocycles with subheterocyclic rings: (c) Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513. Multidentate macrocycles: (d) Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Ibid.* **1974**, *74*, 351. Annulenes: (e) Sondheimer, F. *Acc. Chem. Res.* **1972**, *5*, 8.

[5] Representative examples include: (a) Doskotch, R. W.; El-Feraly, F. S. *J. Org. Chem.* **1970**, *35*, 1928. (b) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147. (c) Vanhaelen-Fastre, R. *J. Pharm. Belg.* **1972**, *27*, 683. (d) Herz, W.; Wahlberg, I. *J. Org. Chem.* **1973**, *38*, 2485. (e) Lee, K.-H.; Kimura, T.; Okamoto, M.; Cowherd, C. M.; McPhail, A. T.; Onan, K. D. *Tetrahedron Lett.* **1976**, *1051*. (f) Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573, and pertinent literature citations given in ref 3a.

[6] Dihydrocostunolide: (a) Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736. (b) Fujimoto, Y.; Shimizu, T.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 2041. (c) Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717. Costunolide: ref 6c. Presiocalamendiol: (d) Kato, K.; Hirata, Y.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1324. (e) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186. Dihydronovanin: (f) Watanabe, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1972**, 698. Hedycaryol: (g) Wharton, P. S.; Sunden, C. E.; Johnson, D. W.; Kluender, H. C. *J. Org. Chem.* **1972**, *37*, 34. (h) Kodama, M.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1976**, 1121. (i) Kodama, M.; Yokoo, S.; Yamada, H.; Itô, S. *Ibid.* **1978**, 3121. Acoragermacrone: ref 6e. Periplanone-B: (j) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. Linderalactone, isolinderalactone, and neolinderalactone: (k) Gopalan, A.; Magnus, P. *Ibid.* **1980**, *102*, 1756.

[7] For reviews and recent studies pertinent to synthesis methodology in this area, see: (a) Marshall, J. A. *Rec. Chem. Prog.* **1969**, *30*, 3. (b) Story, P. R.; Busch, P. *Adv. Org. Chem.* **1972**, *8*, 67. (c) Brown, J. M.; Cresp, T. M.; Mander, L. N. *J. Org. Chem.* **1977**, *42*, 3984. (d) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 880, and ref 3 and 4.

[8] (a) Yoshioka, H.; Mabry, T. J.; Miller, H. E. *J. Chem. Soc., Chem. Commun.* **1968**, 1679. (b) Yoshioka, H.; Mabry, T. J. *Tetrahedron* **1969**, *25*, 4767. (c) Yoshioka, H.; Mabry, T. J.; Higo, A. *J. Am. Chem. Soc.* **1970**, *92*, 923.

[9] For a recent compilation, see ref 3a.

[10] (a) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267. (b) For a related independent study, see: Lange, G. L.; Huggins, M.-A.; Neidert, E. *Tetrahedron Lett.* **1976**, 4409. (c) A general treatment of this concept is given in ref 7b. Recent studies include: (d) Williams, J. R.; Callahan, J. F. *J. Chem. Soc., Chem. Commun.* **1979**, 404, 405. (e) Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373. (f) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. (g) Wender, P. A.; Letendre, L. J. *Ibid.* **1980**, *45*, 367. For related intramolecular examples, see: (h) Salomon, R. G.; Coughlin, D. J.; Easler, E. M. *J. Am. Chem. Soc.* **1979**, *101*, 3961. (i) Mehta, G.; Veera Reddy, A.; Srikrishna, A. *Tetrahedron Lett.* **1979**, 4863.

0002-7863/80/1502-6340$01.00/0 © 1980 American Chemical Society

countered β-C-8 stereochemistry[3a] while the complementary stereochemistry found, for example, in isabelin was expected to arise from a halohydrin-based epoxidation. The preparation of this enone proved, however, to be eventful in that introduction of unsaturation into the readily available photoadduct **4**[1a,10f] (Scheme II) could not be efficiently effected through the use of various conventional procedures, including dehydrobromination of **5**[11] and oxidative elimination based on seleno ketone **6**. However, the complications[12] encountered in these eliminations based on the simultaneous trigonalization of two sp^3 centers of an already strained ring system were effectively circumvented through the use of a sequential trigonalization strategy. Thus, ketone **4** was converted to its silyl enol ether which was smoothly oxidized with palladium(II) acetate[13] to provide the desired enone (**3**) in 84% overall yield.

The aforenoted preference for β-face reagent addition to enone **3** was revealed at this point in both its direct epoxidation with sodium hypochlorite/water/pyridine,[14] which gave epoxides **7** and **8** in the ratio 1:20, and its reaction with chlorine-saturated water[15] followed by treatment of the crude chlorohydrins with potassium carbonate/acetone, which served to stereoselectively provide the epoxide required for isabelin (**7**:**8** = 4.5:1). Alternatively, epoxide **7** could be obtained in a completely stereocontrolled fashion[16] and in an overall yield of greater than 70% via the sequence **3** → **9** → **10** → **7**. The efficient sodium borohydride/cerium(III) chloride[17] reduction of enone **3** in this sequence is noteworthy since the use of sodium borohydride alone gave largely a lactone product arising from 1,4- followed by 1,2-hydride addition.

Reductive cleavage of epoxy ketone **7** with dimethylcopper lithium[18] followed by addition of allyl iodide gave the product of exclusive β-face alkylation, ketone **11**, and unalkylated reduction product **12** in the ratio of ca. 3:4.5, respectively (combined yield ca. 70–80%). While repeated efforts to suppress the proton-transfer process leading to **12** were unsuccessful, the quantitative recycling of this compound placed the adjusted yield of **11**[19] at >50%. Reductive lactonization of ketone **11** provided the hydroxy lactone **13** (85%) which, upon ozonolysis, was converted to a mixture of unstable lactol **14** and its open-chain isomer, hydroxyaldehyde **15**. Oxidation of this mixture with Fetizon's reagent[20] afforded the highly crystalline dilactone **16** in 88% overall yield from hydroxy lactone **13**. Methylenation[21a] of dilactone **16** gave photoisobelin (**2**, 40%) along with a comparable amount of bis[(dimethylamino)methyl] product.[21b] The photoisabelin thus obtained proved to be identical with an authentic sample independently prepared by irradiation of natural isabelin according to the procedure of Yoshioka, Mabry, and Higo.[8c] Finally, pyrolysis of **2** gave, in quantitative yield, a mixture of (±)-isabelin (**1**) and (±)-pyroisabelin (**17**) in a ratio (1:2, respectively) which is similar to that obtained previously in the pyrolysis of dehydrophotoisabelin.[8c,22]

In summary, the described chemistry allows for the synthesis of (±)-isabelin (**1**) with complete control over the C-6, C-7, and C-8 stereocenters in a 13-operation sequence. This strategy, the less selective but shorter (10 operations) chlorohydrin sequence, and the availability of the complementary epoxides **7** and **8** should prove useful in establishing a general approach to germacradiene synthesis and in extending the metathesis concept to other natural and nonnatural objectives.

Acknowledgment. We thank P. R. Neuman and T. J. Mabry for a sample of natural isabelin. This investigation was supported by Grant CA 21136, awarded by the National Cancer Institute, DHEW.

---

(11) All new compounds reported were homogeneous by TLC and gave satisfactory IR and NMR spectra and exact mass or combustion analyses. Partial analytical data for selected intermediates are as follows. Enone **3**: NMR ($CDCl_3$) δ 6.97 (ddd, J = 2.9, 6.1, 10.2 Hz, 1 H), 6.13 (dd, J = 2.8, 10.2 Hz, 1 H), 3.06 (brs, 1 H); IR (film) 1720, 1670 cm^{-1}. Lactone **9**: mp 60–61 °C; NMR ($CDCl_3$) δ 5.72–6.10 (m, 2 H), 4.88 (dd, J = 1.7, 9.2 Hz, 1 H), 2.72 (d, J = 9.2 Hz, 1 H); IR (CCl_4) 1760, 1665 cm^{-1}. Bromohydrin **10**: mp 141–142 °C; NMR ($CDCl_3$) δ 4.99 (brd, J = 9.5 Hz, 1 H), 4.38 (m, 2 H), 2.88 (d, J = 9.5 Hz, 1 H); IR (KBr) 1740 cm^{-1}. Epoxy ketone **7**: mp 76–77 °C; NMR ($CDCl_3$) δ 3.58 (m, 1 H), 3.38 (dd, J = 1.0, 4.5 Hz, 1 H), 2.78 (d, J = 1.0 Hz, 1 H). Keto ester **11**: NMR δ 3.84 (br m, 1 H), 2.83 (s, 1 H); IR (film) 3400, 3050, 1720, 1690, 1640 cm^{-1}. Hydroxy lactone **13**: mp 94.5–95.5 °C; NMR ($CDCl_3$) δ 4.57 (d, J = 8.7 Hz, 1 H), 3.81 (m, 1 H), 2.67 (d, J = 8.7 Hz, 1 H); IR (KBr) 3400, 3050, 1735, 1640 cm^{-1}. Lactol **14**/aldehyde **15**: NMR ($CDCl_3$) δ 9.78 (s), 5.59 (m, 1 H), 4.66 (dd, J = 8.8 17.5 Hz), 4.49 (dd, J = 1.6, 8.7 Hz, 1 H); IR (CH_2Cl_2) 3600, 1760, 1750, 1720 cm^{-1}. Dilactone **16**: mp 180 °C; NMR ($CDCl_3$) δ 4.70 (t, J = 9 Hz, 1 H), 3.97 (ddd, J = 6, 6, 12 Hz, 1 H), 2.73 (d, J = 9.4 Hz, 1 H); IR ($CHCl_3$) 1780, 1760 cm^{-1}. Pyroisabelin **17**: NMR ($CDCl_3$) δ 6.96 (d, J = 1.8 Hz, 1 H), 6.37 (d, J = 3.6 Hz, 1 H), 5.90 (d, J = 3.3 Hz, 1 H), 4.16 (dt, J = 3.5, 10.6 Hz, 1 H); IR ($CHCl_3$) 1760, 1665 cm^{-1}.

(12) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(13) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 496.

(14) For studies on the utility of this epoxidation method, see: Jakubowski, A. A.; Guziec, F. S.; Tishler, M. *Tetrahedron Lett.* **1977**, *2399*. Wellman, G. R.; Lam, B.; Anderson, E. L.; White, E. *Synthesis* **1976**, 547.

(15) Hendickson, J. B.; Bogard, T. L. *J. Chem. Soc.* **1962**, 1678. We thank Professor Hendrickson for a discussion of this earlier publication.

(16) In the transformation **9** → **10** an allylic bromide byproduct was obtained in 8%.

(17) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

(18) Szajewski, R. P. *J. Org. Chem.* **1978**, *43*, 1819.

(19) The results of an alternative means for effecting this alkylation based on the reaction of enolonium ion equivalents with a nucleophilic C-7 appendage will be disclosed in due course.

(20) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171.

(21) (a) Danishefsky, S.; Schuda, P. F.; Kitihara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066. (b) The formation of a bis adduct is a problem which is, for the most part, peculiar to small-scale reactions.

(22) When compared with our previous studies (ref 10a,f,g) and the mechanistic work cited therein, this result is synthetically and mechanistically noteworthy in that only medium-ring Cope isomers are formed, and direct entry into the *E*,*E* series can be realized, presumably due to the influence of the C-7, C-8 lactone on the relative energies for the pro-*E*,*E* (boatlike) and pro-*E*,*Z* (chairlike) transition states required for fragmentation.

(23) Fellow of the Alfred P. Sloan Foundation, 1979–1981.

(24) National Science Foundation Fellow, 1975–1978.

Paul A. Wender,*[23] John C. Lechleiter[24]
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received May 12, 1980

Two-Dimensional Coordination Polymers of Rhodium(1+) with Rigid Collinear Diisocyanide Bridges and Stacked Layers Arrangement

Sir:

Interaction of the coordination sphere of metals with stereochemically rigid nonchelating bidentate ligands should in theory provide a mechanism for template polymerization. For instance, the application of rigid bidentate ligands, capable of forming collinear bridges between metal nuclei, to the coordination symmetries $D_{\infty h}$, D_{4h}, and O_h is a conceivable route to well-defined one-, two-, and three-dimensional coordination polymers of the type $[M(bridge)_m]_n$, where m = 1, 2, and 3, respectively. Conceptually, terminally coordinated[1] rigid diisocyano bridging ligands constitute an excellent model system on which to examine the effects of template polymerization. The rigid bridging geometries of such bidentate ligands can conveniently be divided into three main categories, considering metal to isocyanide bonds as vectors: (i) collinear (e.g., 1,4-diisocyanobenzene), (ii) bent (e.g., 1,3-diisocyanobenzene), and (iii) parallel (e.g., 1,5-diisocyanonaphthalene), depending on the relationship between the vectors of the bridging units. In the current communication, we exemplify the concept of template polymerization by reporting the formation of some novel coordination polymers of rhodium(1+) with certain collinear diisocyano linkages.

---

(1) Review articles covering the coordination properties of isocyanides: L. Malatesta and F. Bonati, "Isocyanide Complexes of Metals", Wiley, London, 1969; P. M. Treichel, *Adv. Organomet. Chem.*, **11**, 21 (1973); F. Bonati and G. Minghetti, *Inorg. Chim. Acta*, **9**, 95 (1974).

0002-7863/80/1502-6341$01.00/0 © 1980 American Chemical Society