because of difficulty in their quantitative separation by TLC or GC. All product ratios and structures were established by 400-MHz ^{1}H NMR spectrometry with decoupling; all pure compounds as well as regioisomer mixtures were further characterized by mass spectrometric analyses and infrared spectra. Control experiments involving the substrate **4** showed very similar isomer ratios at 2 h vs. 20 h of reaction time. The yields in Table I refer to isolated yields after chromatography. They are not optimized, and some product loss from volatility may have occurred.

The data of Table I reveal this cyclization to be a powerful and often regioselective method, with some specific limitations. It appears that in the cyclohexene series a second substituent (e.g., CH_3 or COOR) on the carbon bearing the alkenyl chain is essential for cyclization to compete with conjugated enone formation. Thus, in contrast to the smooth cyclization of **4**, the substrate 3-allyl-2-(trimethylsiloxy)cyclohexene with $Pd(OAc)_2$ under our conditions gave a mixture of conjugated enone and starting ketone, but no bicyclic product. The reason for this may be conformational: an axial side chain is required to form the new bridge. It is also noteworthy that for those cases where a new six-membered ring bridge is generated, the double bond in the new bridge forms predominantly away from the more highly substituted bridgehead carbon.

Compounds **8** and **9** in Table I show that excellent yields of spirobicycloalkenones can be obtained by cyclization of suitable precursors. In the case of the Me_3Si enol ether **8**, the structures of the spirocyclic enones **14** and **15** formed as a 3:2 mixture were confirmed by the following stereoconvergent transformations: (a) catalytic reduction of the mixture H_2, Pd–C, and EtOAc at 1 atm and 25 °C to give exclusively the known spiro[4.5]decan-6-one;[9] (b) hydroboration–oxidation (10 equiv of BH_3–THF, in THF, 0 °C; then made alkaline with H_2O_2 followed by PCC oxidation) to give 70% of spiro[4.5]decane-2,6-dione, mp 47–48 °C (hexane).[10]

When an allyl substituent is γ to the trimethylsiloxy carbon, the $Pd(OAc)_2$ closure leads to *bridged five-membered rings* (compounds **10** and **11**). In the simplest case of **10**, the cyclization gives in 65% yield a 2:1 ratio of the exocyclic and endocyclic olefins **16** and **17**. For the Me_3Si dienol ether **11** only the exocyclic olefin **18** is observed, possibly reflecting the higher strain energy of the endocyclic olefin in this system.

An intriguing example of the regiospecificity of the reaction is the cyclization of the Me_3Si dienol ether **12**. The sole cyclization product is a conjugated enone (IR ν_{CO} 1680 cm^{-1}; UV λ_{max} (MeOH) 234 nm, ϵ 11 600) which can be shown by mass and 400-MHz ^{1}H NMR spectroscopy to have the structure **19**.[11] Here a new six-membered ring bridges the allyl terminus to the γ position of the original conjugated enone system.

Although the full scope and mechanism of these novel cyclizations remain to be defined, it is already evident that these simple reactions offer potential entry to a variety of bridged and spirocyclic systems. Applications of this methodology to the synthesis of phyllocladene,[12] quadrone,[13] and other polycyclic natural products are in progress.

Acknowledgment. Partial support of this work by Grant CA-18846, awarded by the National Cancer Institute (USPHS) is gratefully acknowledged. We are indebted to Jen Chen and Pawel Fludzinski for the synthesis of several of the ketone precursors to the Me_3Si enol ether substrates in Table I.

Registry No. 4, 80953-94-2; **5**, 80953-95-3; **6**, 80953-96-4; **7**, 80953-97-5; **8**, 80953-98-6; **9**, 80953-99-7; **10**, 80954-00-3; **11**, 80954-01-4; **12**, 80954-02-5; **13**, 4696-33-7; **14**, 61765-59-1; **15**, 14054-26-3; **16**, 80954-03-6; **17**, 80954-04-7; **18**, 80954-05-8; **19**, 80954-06-9; 1-methyl-9-oxobicyclo[3.3.1]non-3-ene, 80954-07-0; 1-methyl-9-oxobicyclo[3.3.1]non-3-ene, 80954-08-1; 1,4-dimethyl-9-oxobicyclo[3.3.1]non-3-ene, 4071-70-9; 1,4-dimethyl-9-oxobicyclo[3.3.1]non-3-ene, 80954-09-2; 1-methyl-4-methylene-9-oxobicyclo[3.3.1]nonane, 80954-10-5; 4-methylenespiro-[4.5]decan-6-one, 42988-49-8; 4-methylspiro[4.5]dec-3-ene-6-one, 61765-60-4; 4-methylspiro[4.5]dec-2-ene-6-one, 80954-11-6; $Pd(OAc)_2$, 3375-31-3.

(9) Hart, H.; Leiner, L. R. *J. Org. Chem.* **1967**, *32*, 2669. Quadrat-i-Khuda, M.; Ray, A. S. *J. Indian Chem. Soc.* **1939**, *16*, 525. Our semicarbazone, mp 187–189 °C (lit. mp 187–190 °C, 188–190 °C), contained 62.94% C and 9.07% H.

(10) Spiro[4.5]decane-2,6-dione: IR ν_{CO} 1775, 1715 cm^{-1}; ^{1}H NMR δ 2.80 (1 H, d, J = 18 Hz), 2.57–2.24 (4 H, m), 2.01 (1 H, d, J = 18 Hz), 1.96–1.58 (8 H, m). For a related spirodiketone, see: Ganter, C.; Warszawski, R.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1963**, *46*, 320.

(11) Compound **19**: ^{1}H NMR ($CDCl_3$) δ 5.90 (1 H, ddd, J = 9, 6, 2 Hz), 5.79 (1 H, s), 5.54 (m, 1 H), 2.98 (1 H, dd, J = 7.5, 6 Hz), 2.86 (1 H, dd, J = 15, 2 Hz), 2.15 (1 H, dd, J = 15, 4 Hz), 2.52–2.42 (2 H, m), 2.09–1.62 (6 H, m).

(12) Briggs, L. H.; Cain, B. F.; Cambie, R. C.; Davis, B. R. *J. Chem. Soc.* **1962**, 1840 and references cited therein.

(13) Rainieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499.

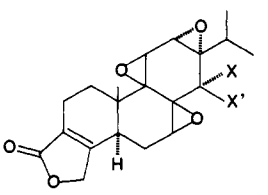
Biogenetic-Type Total Synthesis of (±)-Triptonide and (±)-Triptolide

E. E. van Tamelen* and T. M. Leiden

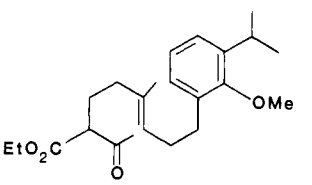
Department of Chemistry, Stanford University
Stanford, California 94305

Received December 17, 1981

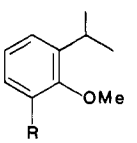
Triptolide (**1**) and triptonide (**2**), potent cytotoxic agents occurring in *Tripterygium wilfordii* Hook F,[1] have been the objectives of considerable synthetic effort during recent years.[2-4] In a departure from previous approaches, we have carried out an abbreviated, facile biogenetic-type total synthesis, featuring cyclization of a geranylgeraniol surrogate (**3**), in which a β-keto ester initiator serves as a covenient precursor of the unsaturated lactone unit and an appropriately substituted benzenoid unit acts not only as a terminator but also constitutes the framework for the polyepoxide moiety of the natural product system.



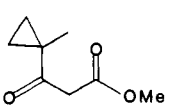
1 X=H; X'=OH
2 X,X'=O



3



4 R=H
5 R=CH_2OH
6 R=CH_2Br



7

2-Isopropylanisole (**4**) (obtained in 90% yield by alkylation of 2-isopropylphenol with NaH/MeI in THF at room temperature) was *o*-metalated with *n*-BuLi in TMEDA at room temperature, after which reaction with formaldehyde (generated from paraformaldehyde at 140 °C) gave rise to benzylic alcohol **5** (60% from **4**).[5] The corresponding bromide (**6**) (produced in 90% yield

(1) Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7194.

(2) Buckanin, R. S.; Chen, S. J.; Frieze, D. M.; Sher, F. T.; Berchtold, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 1200 and preceding publications.

(3) Koike, H.; Tokoroyama, T. *Chem. Lett.* **1979**, 333; *Tetrahedron Lett.* **1978**, 4531.

(4) (a) van Tamelen, E. E.; Demers, J. P.; Taylor, E. G.; Koller, K. *J. Am. Chem. Soc.* **1980**, *102*, 5424 and preceding publications. (b) Garver, L. C.; van Tamelen, E. E. *Ibid.* **1982**, *104*, 867.

(5) **5**: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 6 H, J = 6.9 Hz, $CHMe_2$), 2.25 (br t, 1 H, J = 5.4 Hz, O*H*), 3.37 (sept, 1 H, J = 6.9 Hz, $CHMe_2$), 3.79 (s, 3 H, OCH_3), 4.72 (br d, 2 H, J = 5.4 Hz, CH_2O), 7.11–7.32 (m, 3 H, aromatic H).

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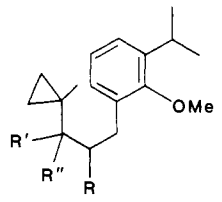
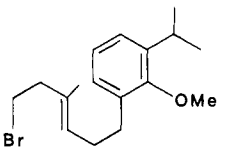
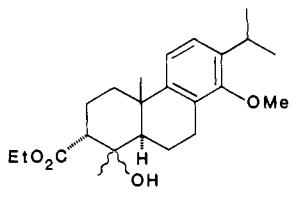
by the action of PBr_3 in ether at 0 °C) was used to alkylate (NaH; THF; 0 °C to room temperature) the cyclopropyl ketoester **7**,[6] thereby generating **8** (99%).[7] Removal of the ester function by



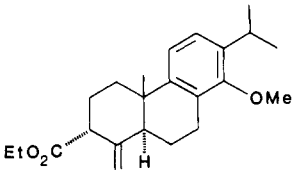
8 R=COOMe; R',R''=O
9 R=H; R',R''=O
10 R=R'=H; R''=OH



11



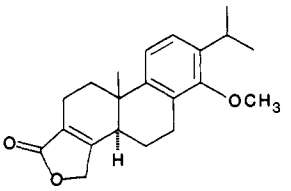
12



13

means of $Ba(OH)_2$ saponification and concurrent decarboxylation (H_2O/Et_2O for 17 h at 90 °C) led to ketone **9** (92%), which was reduced with LAH (dry ether, 0 °C) to the cyclopropyl carbinol **10**. Conversion of the latter to homoallylic bromide **11**[8] was accomplished in 70% yield by the method of Julia (LiBr, PBr_3, collidine in Et_2O at −40 to 0 °C; then $ZnBr_2$ in Et_2O at 0 °C).[9] Alkylation of ethyl acetoacetate with bromide **11** (LiH; DMF; 75 °C)[10] gave rise to the substituted β-ketoester (**3**)[11] (90%) desired for cyclization.

In the best procedure for cyclization, β-ketoester **3** was exposed to the action of $SnCl_4$ in CH_2Cl_2 at 0 °C for 1–1.5 h, generating tricycle **12**,[12] which was transformable without purification to the unsaturated ester **13**[12] by treatment with 7–8 equiv of $MeSO_2Cl$ and 10 equiv of $(C_2H_5)_3N$ in CH_2Cl_2 at 0 °C. In order to generate the butenolide moiety, crude olefinic ester **13** was directly oxidized (*m*-$ClC_6H_4CO_3H$; CH_2Cl_2; room temperature) to the corresponding β,γ-epoxy ester; subjection of the latter, without isolation, to elimination conditions (*n*-C_4H_9Li/*i*-C_3H_7NH; −78 °C) presumably generates the γ-hydroxy α,β-unsaturated ester, which cyclizes *in situ* to the (±) tetracycle **14**[14] (51% from keto ester



14

3), identical in all respects (NMR, IR, and mass spectroscopy and TLC) with material of structure **14** produced by means of earlier routes.[4] In view of the prior conversion of **14** to the corresponding 7-ketone[4] and thence to (±)-triptonide (**2**) and (±)-triptolide (**1**),[2,4] the transformations described herein constitute a new synthesis of these natural products (in the racemic form).[15] Overall, this synthesis of **14** requires 12 steps from available materials, necessitates the purification of only 4 intermediates, and proceeds in a yield of ~15%, compared to 20–30 steps and ~0.3–15% yields in prior approaches.[4]

Acknowledgment. Grant support from the National Science Foundation (CHE-8002661) is gratefully acknowledged.

Registry No. 1, 73414-46-7; **2**, 73465-88-0; **3**, 80865-60-7; **4**, 2944-47-0; **5**, 80865-61-8; **6**, 80865-62-9; **7**, 61185-33-9; **8**, 80865-63-0; **9**, 80865-64-1; **10**, 80865-65-2; **11**, 80865-66-3; **12**, 80865-67-4; **13**, 80865-68-5; **14**, 73414-41-2; 2-isopropylphenol, 99-89-8; ethyl acetoacetate, 141-97-9.

(6) Rhoads, S. J.; Gilbert, J. C.; Decora, A. W.; Garland, T. R.; Spangler, R. J.; Urbigkit, M. J. *Tetrahedron* **1963**, *19*, 1625.

(7) **8**: ^1H NMR ($CDCl_3$) δ 0.60 (m, 2 H, cyclopropyl H), 1.21 (s, 3 H, CH_3), 1.11, 1.25 (dd, 6 H, J = 3.6, 6.9 Hz, $CHMe_2$), 1.20 (m, 2 H, cyclopropyl H), 3.17 (m, 2 H, CH_2), 3.21 (m, 1 H, $CHMe_2$), 3.67 (s, 3 H, CO_2Me), 3.74 (s, 3 H, OMe), 4.0 (m, 1 H, CH), 6.91–7.22 (m, 3 H, aromatic H).

(8) **11**: ^1H NMR ($CDCl_3$) δ 1.23 (d, 6 H, J = 6.9 Hz, $CHMe_2$), 1.58 (br s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 5.33 (br t, 1 H, vinyl H), 7.0–7.2 (m, 3 H, aromatic H).

(9) Julia, M.; Julia, S.; Tchen, S.-Y. *Bull. Soc. Chim. Fr.* **1961**, 1849.

(10) Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065.

(11) **3**: ^1H NMR ($CDCl_3$) δ 1.23 (d, 6 H, J = 6.9 Hz, $CHMe_2$), 1.27 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.57 (br s, 3 H, CH_3), 2.20 (s, 3 H, C(O)CH_3), 3.74 (s, 3 H, OMe), 4.19 (quart, 2 H, J = 7.1 Hz, $CO_2CH_2\mu$), 5.23 (br t, 1 H, vinyl H), 7.0–7.2 (m, 3 H, aromatic H).

(12) Sterochemical assignments are based on comparison of the NMR spectrum of crude tricyclic ester with the spectra of well-characterized counterparts encountered in earlier, related studies.[13]

(13) van Tamelen, E. E.; Taylor, E. G. *J. Am. Chem. Soc.* **1979**, *102*, 1202.

(14) **14**: mp 175.5–176 °C; IR (CCl_4) 2962, 1763, 1678, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 3 H, CH_3), 1.22 (d, 3 H, J = 6.8 Hz, $CHMe_2$), 1.23 (d, 3 H, J = 6.8 Hz, $CHMe_2$), 3.30 (sept, 1 H, J = 6.8 Hz, $CHMe_2$), 3.74 (s, 3 H, OCH_3), 4.7, (m, 2 H, OCH_2), 7.11(s, 2 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 174.0 (=O), 162.9 (C=C), 1.55.5, 144.1, 139.1, 128.0 (aryl), 124.8 (C=C), 124.0, 120.2 (aryl), 70.4 (OCH_2), 60.4 (OMe).

(15) For the production of tripdiolide by tissue culture of *Tripterygium wilfordii* see: Kutney, J. P.; Beale, M. H.; Salisbury, P. J.; Sindelar, R. D.; Stuart, K. L.; Worth, B. R.; Townsley, P. M.; Chalmers, W. T.; Donnelly, D. J.; Nilsson, K.; Jacoli, G. G. *Heterocycles* **1980**, *14*, 1465.

*Book Reviews**

Polymer Catalysts and Affinants—Polymers in Chromatography. Edited by B. Sědlacěk (Institute of Macromolecular Chemistry, Prague), C. G. Overberger (University of Michigan) and H. F. Mark (Polytechnic Institute of New York). John Wiley and Sons, Inc., New York. 1980. v + 254 pp.

This is No. 68 in the Polymer Symposium Series of the Journal of Polymer Science and represents part of the proceedings of an IUPAC meeting on macromolecules held in 1978 in Prague. It is a collection of 28 papers ranging in length from 6 to 12 pages and covering topics in two somewhat related fields. The first field includes examples of the use of polymeric or polymer-bound catalysts, while the second is concerned with affinity chromatography and applications of polymers in chromatography. Of the 28 papers, most are written by authors from European and Communist countries, and most are concerned with chromatography. Much of the work described is reasonably up-to-data as of 1978 and ranges in quality from acceptable to excellent. The subjects range from polymer-bound transition metal catalysts to immobilized enzymes and whole cells, and from chromatography of peptides and nucleic acid derivatives to TLC of synthetic macromolecules. A number of papers deal with various aspects of gel permeation chromatography and there are even two papers on inverse GC. While this book is a must for all reference and university libraries, the concise nature of the reports will make this book of specific interest only to those workers in the titled fields.

Lon J. Mathias, *University of Southern Mississippi*

Techniques and Applications of Path Integration. By Lawrence S. Schulman. John Wiley & Sons, New York. 1981. xv + 359 pp. $31.95.

Path integration arose as a mathematical technique in quantum the-

* Unsigned book reviews are by the Book Review Editor.