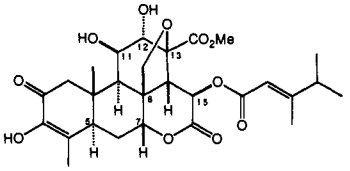
Total Synthesis of (±)-Bruceantin

James M. VanderRoest and Paul A. Grieco*

Department of Chemistry
Indiana University
Bloomington, Indiana 47405

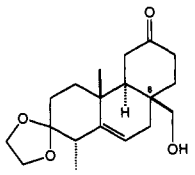
Received March 18, 1993

Since the isolation and characterization of bruceantin (**1**) by Kupchan and associates[1] over 20 years ago, synthetic organic chemists worldwide have been engaged in efforts to prepare **1** and closely related quassinoids via total synthesis.[2] We detail below the first total synthesis of (±)-bruceantin (**1**).[3]



1

The synthesis of **1** commences with tricyclic ketone **2**, which had been recognized over 10 years ago by a number of synthetic groups[4] as a logical starting point for a synthesis of bruceantin.



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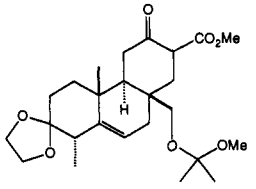
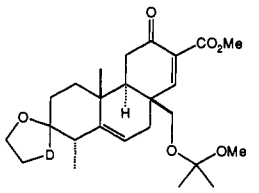


3

Our strategy for the conversion of **2** into **1** required transformation of **2** via β-keto ester **3** into the activated tricyclic enone **4**, which would permit introduction of a two-carbon acetic acid unit at C(14). Toward this end, the hydroxymethyl group at C(8) in **2** was protected (PPTS,[5] 2-methoxypropene, 0 °C, 30 min) and subsequently subjected to carbomethoxylation [NaH, $(MeO)_2CO$, MeOH(catalyst), THF, reflux, 18 h], giving rise to **3** in 88% overall yield. Selenenylation (NaH, PhSeCl, THF, 0 °C, 45 min) of β-keto ester **3** followed by oxidation (MCPBA, THF, −78 °C → 0 °C) and elimination of benzeneselenenic acid afforded (81%) tricyclic enone **4**, mp 134–135 °C. All attempts to add a number of acetic acid equivalents in a Michael fashion to **4** either thermally or under conventional Lewis acid catalysis failed. However, treatment of a 0.1 M solution of activated enone **4** in 1.0 M lithium perchlorate–dimethoxyethane[6] with excess 1-methoxy-1-(*tert*-butyldimethylsiloxy)ethylene at 40 °C for 12 h gave



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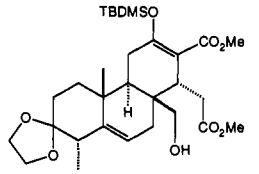
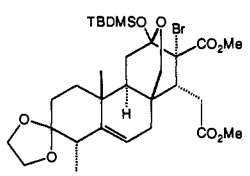
rise, after cleavage (MeOH, PPTS,[5] 0 °C, 1.5 h) of the 1-methyl-1-methoxyethyl ether, to **5** in 81% overall yield.



5

Our synthetic plan for elaboration of the C(8), C(13) epoxymethano bridge was based upon a serendipitous observation made some years ago in our laboratory in connection with quassinoid model studies.[7] Bromination (NBS, THF, 0 °C, 2 h) of **5** led in 97% yield to the crystalline bromosilylated hemiketal **6**, mp 162–164 °C, which upon heating [DMF, collidine (10 equiv), 130 °C, 23 h] gave rise (80%) to **7** possessing the intact C(8), C(13) epoxymethano bridge of bruceantin.



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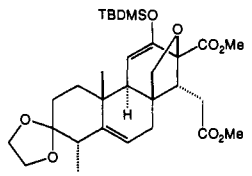

7

Introduction of the C(11), C(12) *trans* diaxial diol unit into ring C was realized via an eight-step sequence, as outlined in Scheme I. Cleavage (MeOH, KF) of the silyl enol ether in **7** afforded in quantitative yield tetracyclic ketone **8**, mp 180–182 °C, which in straightforward fashion was subjected to reduction and selective protection of the two primary hydroxyl groups as *tert*-butyldiphenylsilyl ethers, giving rise to **9**. Oxidation of the secondary hydroxyl in **9** provided the corresponding C(12) ketone, which was transformed into tetracyclic olefin **10**, mp 102–105 °C, via treatment of its derived tosylhydrazone with excess lithium diisopropylamide. Exposure of **10** to osmium tetraoxide generated selectively the corresponding C(11), C(12) *cis* α-oriented vicinal diol in 85% yield. Subsequent oxidation of the less hindered C(11) hydroxyl afforded tetracyclic ketone **11**, mp 174–176 °C, which upon reduction with sodium borohydride gave rise to **12**, mp 100–103 °C.

With all the functionality of ring C in place, attention was focused on elaboration of the δ-lactone ring possessing a hydroxyl group at C(15). Protection (MOMCl, *i*-Pr_2NEt, $ClCH_2CH_2Cl$, 48 °C, 18 h) of the *trans*-oriented hydroxyl groups at C(11) and C(12) as their methoxymethyl ethers followed by allylic oxidation (CrO_3·3,5-dimethylpyrazole,[8] −25 °C, 4 h) gave rise (52%) to tetracyclic enone **13**. Reduction (Li, NH_3, *t*-BuOH, −78 °C, 1.25 h; isoprene quench) of the α,β-unsaturated ketone in **13**

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(2) Grieco, P. A.; Nargund, R. P.; Parker, D. T. *J. Am. Chem. Soc.* **1989**, *111*, 6287 and references cited in ref 3. Also see: Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 2593. Sasaki, M.; Murae, T.; Matsuo, H.; Konosu, T.; Tanaka, N.; Yagi, K.; Usuki, Y.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3587. Sasaki, M.; Murae, T.; Takahashi, T. *Tetrahedron Lett.* **1988**, *29*, 5953. Sasaki, M.; Murae, T. *Ibid.* **1989**, *30*, 355. Stojanac, H.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853.

(3) For a relay synthesis of bruceantin, see: Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528.

(4) (a) Snitman, D. L.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 187. (b) Snitman, D. L.; Himmelsbach, R. J.; Watt, D. S. *J. Org. Chem.* **1978**, *43*, 4758. (c) Sasaki, S.; Grieco, P. A.; Huffman, J. C.; Callant, P.; Imamura, P. *Ibid.* **1985**, *50*, 4880. (d) Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *Ibid.* **1987**, *52*, 1686.

(5) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(6) Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, *32*, 4665.

(7) Kanai, K.; Zelle, R. E.; Sham, H.-L.; Grieco, P. A.; Callant, P. *J. Org. Chem.* **1984**, *49*, 3867. Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Jaw, J. Y.; Tu, S. *Ibid.* **1987**, *52*, 3346. Grieco, P. A.; Sham, H.-L.; Inanaga, J.; Kim, H.; Tuthill, P. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1345. Also see: Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686.

(8) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

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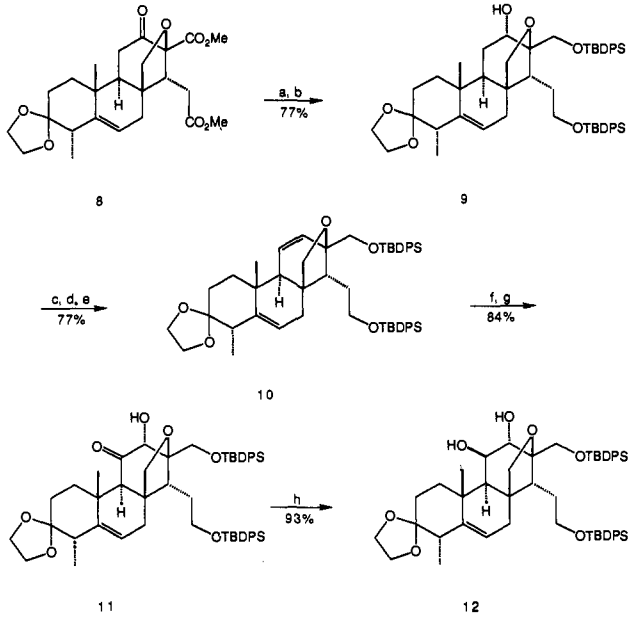
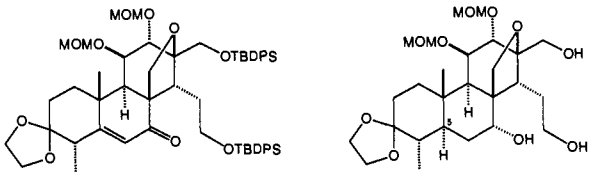
Scheme I. Introduction of the C(11), C(12) *Trans* Diaxial Diol Unit into Tetracyclic Ketone **8**[a]



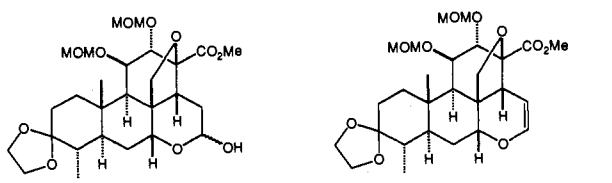
8 9 10 11 12

[a] (a) $LiAlH_4$ (8.0 equiv), THF, 0 °C → room temperature (12 h); (b) TBDPSCl (4.0 equiv), imidazole (8.0 equiv), DMF, 24 h; (c) PCC (3.0 equiv), NaOAc (2.5 equiv), CH_2Cl_2, Celite, 0 °C → room temperature (1.75 h); (d) $TsNHNH_2$ (5.0 equiv), TsOH (0.25 equiv), $MgSO_4$ (10 equiv), THF, 70 h; (e) LDA (10 equiv), DIPA (10 equiv), THF, −78 °C (30 min) → 0 °C (30 min) → room temperature (90 min); (f) OsO_4 (0.8 equiv), pyr, 0 °C, 3 h; $NaHSO_3$, 12 h; (g) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), CH_2Cl_2, −78 °C → room temperature; (h) $NaBH_4$ (5 equiv), MeOH–THF (1:1).



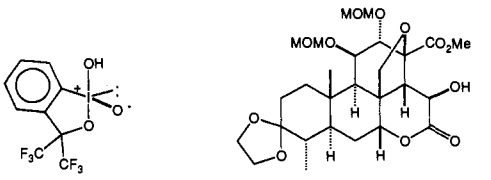
13 14

followed by reduction [1.0 M Super-Hydride (Aldrich) in THF, −78 °C → room temperature, 12 h] of the resultant ketone and subsequent cleavage (TBAF, THF) of the silyl ethers provided in 90% overall yield triol **14**, mp 145.5-147.0 °C, possessing the correct configuration at C(5) and C(7). Triol **14** was transformed via a four-step sequence [(a) $(COCl)_2$ (6.0 equiv), DMSO, −78 °C → room temperature; (b) 8.0 M Jones reagent, acetone, 0 °C, 5 min; (c) CH_2N_2, Et_2O; (d) $NaBH_4$ (2 equiv), EtOH–CH_2Cl_2 (2:1)] into pentacyclic lactol **15** (β:α, 3:2) in 41% overall yield.



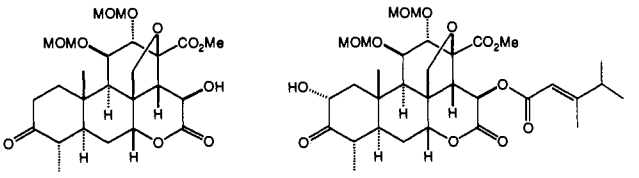
15 16

Exposure of **15** to 2.0 equiv of phosphorus oxychloride in pyridine at 85 °C for 70 min afforded in 86% yield pentacyclic dihydropyran **16**, mp 149.5–151.0 °C. Osmylation [OsO_4 (1.5 equiv), pyr, 0 °C, 45 min; $NaHSO_3$, 12 h] of **16** proceeded smoothly in 94% yield from the desired face of the olefin, giving rise to the corresponding α-hydroxy lactol which upon mild oxidation (1.25 h) employing 2.0 equiv of hydroxyiodinane oxide **17**[9] in methylene chloride gave rise to pentacyclic lactone **18**, mp 221–223 °C, possessing all of the 10 stereogenic centers found in bruceantin.



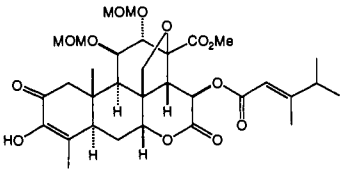
17 18

Completion of the total synthesis of bruceantin necessitated (a) acylation of the C(15) hydroxyl group, (b) introduction of the diosphenol unit into ring A, and (c) deprotection of the hydroxyl groups at C(11) and C(12). Toward this end, **18** was deketalized with 1.0 M hydrochloric acid in tetrahydrofuran, giving rise (85%) to pentacyclic ketone **19**, mp 189.5–191.5 °C.



19 20

Acylation[10] of **19** (0.4 M in THF) employing 2.0 equiv of *trans*-3,4-dimethyl-2-pentenoic acid[11] in tetrahydrofuran containing 2.5 equiv of DCC and 2.0 equiv of 4-(dimethylamino)pyridine provided the corresponding ester, which upon silyl enol ether formation [TMSOTf (5.0 equiv), Et_3N (8.0 equiv), CH_2Cl_2, −10 °C, 30 min] and subsequent oxidation[12] with *m*-chloroperbenzoic acid (2.0 equiv) in methylene chloride at −22 °C for 1 h followed by brief treatment (10 min) with 10 equiv of tetra-*n*-butylammonium fluoride afforded **20** in 70% overall yield. Oxidation of **20** with 2.0 equiv of hydroxyiodinane oxide **17** in methylene chloride (1.2 h) gave rise to a 93% yield of diosphenol **21**.



21

Deprotection [6.0 M HCl:THF:MeOH (2:3:1), 72 h; CH_2N_2] of **21** gave rise (75%) to crystalline racemic bruceantin (**1**), mp 252–255 °C dec. Our racemic sample of bruceantin was identical with a sample of the natural material by comparison of ^1H NMR (500 MHz), IR, and MS spectra and thin-layer mobility in several solvent systems.[13]

Acknowledgment. This investigation was supported by Public Health Service Research Grant CA 28865 from the National Cancer Institute. We are indebted to Professor K.-H. Lee, University of North Carolina at Chapel Hill, for providing us with a sample of natural bruceantin.

Supplementary Material Available: Details of data collection and characterization data for **4–6**, **8–14**, **16**, **17**, **19–21**, and bruceantin (**1**) (9 pages). Ordering information is given on any current masthead page.

(9) The use of **17** as an oxidizing agent in organic chemistry has received virtually no attention. For the preparation of **17**, see: Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. Use of the conventional Dess–Martin reagent on model α-hydroxy lactols led primarily to cleavage.

(10) During the acylation of **19**, approximately 5% of the deconjugated 3-isopropyl 3-butenoate was isolated. This minor impurity could be readily removed by employing 10% silver nitrate impregnated silica gel (200 mesh) purchased from Aldrich.

(11) Okano, M.; Lee, K.-H. *J. Org. Chem.* **1981**, *48*, 1138.

(12) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

(13) All new crystalline compounds have been fully characterized by IR, ^1H NMR, and combustion analysis.