Total Synthesis of 5(*R*)- and 5(*S*)-Polyandrane

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During the course of searching for novel quassinoids possessing solid tumor selectivity from the family *Simaroubaceae* that consists of numerous plant species, the polyandrane bis-lactones, 5(*R*)- and 5(*S*)-polyandrane (**1** and **2**)[1] and 5(*R*)- and 5(*S*)-polyandrol (**3** and **4**),[2] were isolated from *Castela texana* and *Castela polyandra*, respectively, and have been shown by single-crystal X-ray analysis to possess the novel 1,2-seco-1-nor-6(5→10)-*abeo*-picrasan-2,5-olide carbon skeleton. To date only nine naturally occurring polyandranes have been isolated and characterized.[1−3] In view of the structural similarity between the polyandranes and the C_{20} quassinoids, it has been suggested that **1** and **2** are derived biogenetically from chaparrinone (**5**).[4] We detail below the total synthesis of 5(*R*)- and 5(*S*)-polyandrane (**1** and **2**) which constitutes the first published account of a total synthesis among this small group of related bis-lactones.
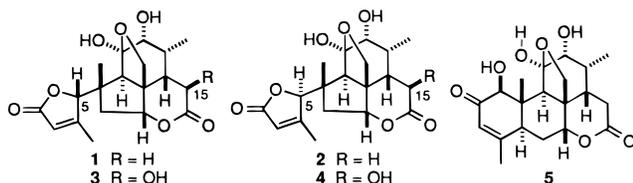
Despite extensive studies which have been carried out over the years on the synthesis of quassinoids,[5] a new approach to the construction of **1** and **2** was necessitated due to the incompatibility of the previous synthetic strategies with the novel seco-nor-picrasane carbon framework of the polyandranes. Thus, the known cis-fused dione **6**,[6] prepared in near quantitative yield (eq 1), served as the logical starting material for the synthesis of **1** and **2**.

The quinone Diels−Alder strategy gives rise to the proper stereochemistry at C(8) and C(14) and provides a cis-fused BC ring system that ensures selective reduction of the C(7) carbonyl

from the convex face of the molecule. Indeed, reduction of **6** with sodium borohydride in ethanol at −15 °C afforded **7** in ca. 70% yield.

Adoption of the Diels−Alder approach depicted in eq 1 requires that the eventual C(9) configuration be inverted at some point in the synthesis and that the six-membered B ring undergo ring contraction. Prior to addressing these two issues, the hydroxyl group in **7** was protected [TBDPSCl, imidazole, DMF, 70%] as its *tert*-butyldiphenylsilyl ether **8** (Scheme 1). Reduction of the lactone carbonyl in **8** followed by exposure to acidic methanol and subsequent reduction of the ester functionality gave rise to tricyclic alcohol **9**, mp 74−76 °C. Protection of the hydroxyl group in **9** followed by hydroboration and subsequent protection of the resultant secondary hydroxyl as its methoxymethyl ether provided **10**. Cleavage of the silyl ether and oxidation[7] of the resultant alcohol afforded tricyclic ketone **11**, which set the stage for inversion of configuration at C(9). As anticipated, exposure of tricyclic ketone **11** to potassium carbonate in methanol at 35 °C gave rise exclusively to tricyclic ketone **12**, mp 71−73 °C, possessing the BC trans ring fusion.[8] Transformation of **12** into the ring contracted ester **13** as a 4:1 mixture with the β-carbomethoxy diastereomer predominating was realized via a photochemically induced Wolff rearrangement[9] on the corresponding α-diazo ketone.[10]

Scheme 1[a]
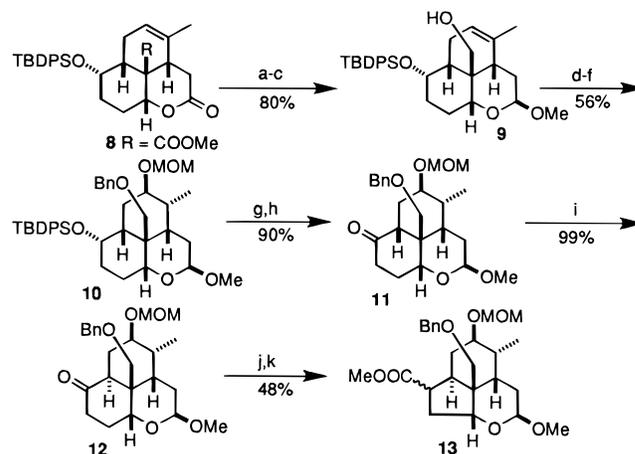
[a] Conditions: (a) *i*-Bu₂AlH, THF, −78 °C, 1 h; (b) THF−MeOH (1:1), concentrated HCl, 10 °C, 16 h; (c) LiAlH₄, THF, 0 °C, 2 h; (d) NaH, BnBr, THF, TBAI, 0 °C, 16 h; (e) 1.0 M B₂H₆ in THF, 0 °C (1 h) → room temperature (3 h); 3.0 N NaOH, H₂O₂, 12 h; (f) MOMCl, *i*-Pr₂NEt, 1,2-dichloroethane, room temperature, 16 h; (g) 1.0 M TBAF in THF, 72 h; (h) TPAP, NMO, CH₂Cl₂, 4-Å MS, 1.5 h; (i) K₂CO₃, MeOH, 35 °C, 30 min; (j) NaH, HCOOEt, Et₂O, EtOH (cat), room temperature, 20 h; TsN₃, Et₂O, 20 h; (k) *hν* (450 W mercury arc lamp, Vycor filter), Et₂O−MeOH (30:1), 1 h.

(1) Bilder, D. M. M.S. Thesis, Indiana University, Bloomington, Indiana, 1998. 5(*R*)-Polyandrane has also been isolated from *Ailanthus malabarica* [see: Aono, H.; Koike, K.; Kaneko, J.; Ohmoto, T. *Phytochemistry* **1994**, *37*, 579].

(2) Grieco, P. A.; VanderRoest, J. M.; Piñeiro-Núñez, M. M. *Phytochemistry* **1995**, *38*, 1463. Piñeiro-Núñez, M. M. Ph.D. Thesis, Indiana University, Bloomington, Indiana, 1996.

(3) Furuno, T.; Ishibashi, M.; Naora, H.; Murae, T.; Hirota, H.; Tsuyuki, T.; Takahashi, T.; Itai, A.; Iitaka, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2484. Yoshimura, S.; Ogawa, K.; Tsuyuki, T.; Takahashi, T.; Honda, T. *Chem. Pharm. Bull.* **1988**, *36*, 841. Itokawa, H.; Qin, X.-R.; Morita, H.; Takeya, K. *J. Nat. Prod.* **1993**, *56*, 1766. Grieco, P. A.; Haddad, J.; Piñeiro-Núñez, Huffman, J. C. *Phytochemistry* **1999**, *50*, 637.

(4) Furuno, T.; Naora, H.; Murae, T.; Hirota, H.; Tsuyuki, T.; Takahashi, T.; Itai, A.; Iitaka, Y.; Matsushita, K. *Chem. Lett.* **1981**, 1797.

(5) Vidari, G.; Ferriño, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539. Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078. Grieco, P. A.; Piñeiro-Núñez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606.

(6) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1174.

(7) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(8) Exclusive conversion of **11** into **12** was not surprising since MMX calculations employing PC MODEL indicated that **12** is more stable than **11** by 4.5 kcal.

(9) Horner, L.; Spietschka, E. *Chem. Ber.* **1955**, *88*, 934. Meinwald, J.; Gassman, P. G. *J. Am. Chem. Soc.* **1960**, *82*, 2857.

(10) Regitz, M.; Menz, F.; Rüter, J. *Tetrahedron Lett.* **1967**, 739.

With the availability of tricyclic ester **13**, efforts were directed at introduction of the C(10) methyl group and elaboration of the ring C functionality. Toward this end, the enolate of ester **13**, generated from lithium diisopropylamide in tetrahydrofuran containing HMPA, was treated with methyl iodide. Workup gave rise to a 90% yield of the alkylated ester **14**, with none of the desired product being detected.
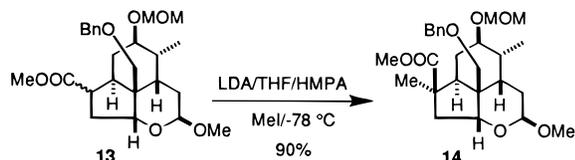
To circumvent the problems associated with direct introduction of a methyl group at C(10), the enolate of **13** was alkylated with benzyloxymethyl chloride which provided **15** in 79% yield as the sole product (Scheme 2). Conversion of ester **15** into the corresponding aldehyde followed by Huang−Minlon reduction[11] afforded **16** in 60% overall yield. With the stereochemistry at C(10) secure, efforts were directed at introduction of the remaining ring C functionality (Scheme 2). Cleavage of the methoxymethyl ether in **16** and oxidation of the resultant alcohol provided tricyclic ketone **17**, mp 112−113 °C. Subjection of **17** to a Shapiro olefination sequence gave rise to the corresponding $\Delta^{11,12}$ olefin, which upon exposure to osmium tetroxide generated vicinal diol **18**, mp 101−103 °C. Selective oxidation[12] of the C(11) hydroxyl followed by protection of the C(12) hydroxyl generated **19** which upon hydrogenolysis gave rise directly to tetracyclic compound **20**, mp 144−145 °C, possessing the complete, intact ring C of the polyandranes.

Scheme 2[a]
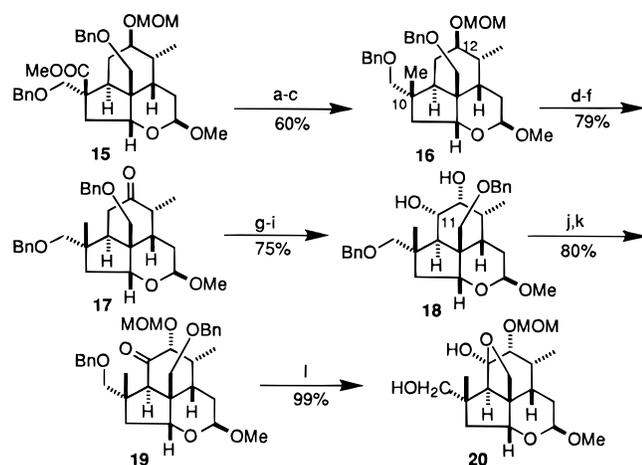
[a] Conditions: (a) LiAlH₄, THF, 0 °C, 1.5 h; (b) TPAP, NMO, CH₂Cl₂, 4-Å MS; (c) NH₂NH₂·H₂O, K₂CO₃, bis(ethylene glycol), 170 °C (2 h) → 210 °C (1.5 h); (d) 5% aqueous HCl−THF (1:1), 55 °C, 11 h; (e) MeOH, concentrated HCl, 10 °C, 2.5 h; (f) TPAP, NMO, CH₂Cl₂, 4-Å MS; (g) TsNHNH₂, MeOH−THF (1:1), room temperature, 3.5 h; (h) LDA (10 equiv), THF, −78 °C (30 min) → 0 °C (1 h) → room temperature (2.5 h); (i) OsO₄ (1.1 equiv), Pyr, room temperature, 3.5 h; NaHSO₃, Pyr, H₂O; (j) (COCl)₂ (2.0 equiv), Me₂SO (4.0 equiv), CH₂Cl₂, −78 °C, 45 min; *i*-Pr₂NEt, −78 °C (45 min) → 0 °C (45 min); (k) MOMCl, *i*-Pr₂NEt, 1,2-dichloroethane, 55 °C, 8 h; (l) H₂, Pd/C, EtOH−THF (2:1), room temperature, 11 h.

Incorporation of the butenolide ring was carried out via a four-step protocol. Dess−Martin oxidation[13] of **20** provided aldehyde **21**, which upon treatment (−100 °C) with the vinyllithium reagent

22[14] gave rise (86%) to **23** as a 2:1 mixture of the C(5) α- and β-hydroxy epimers, respectively. Cleavage [PPTS, MeOH, 40 °C][17] of the tetrahydropyranyloxy group followed by oxidation [Ag₂CO₃ (50 equiv), Celite, benzene][18] afforded (60% overall yield) **24**, mp 185−186 °C, and **25**, mp 193−194 °C, in a ratio of 2:1, which were readily separated by silica gel chromatography. Attempts to prepare **24** and **25** from **23** using the Dess−Martin reagent gave rise (50%) to furan **26**, with none of the desired butenolide being isolated. Equally surprising was the result obtained upon sequential treatment of **23** with pyridinium *p*-toluenesulfonate in methanol (40 °C) followed by exposure to tetra-*n*-propylammonium per-ruthenate/*N*-methylmorpholine *N*-oxide in methylene chloride which provided aldehyde **27** in 80% overall yield. The formation of **27** arises from ring opening of the C(8),C(11) bridged hemiketal followed by oxidation of the resultant hydroxymethyl group at C(8).
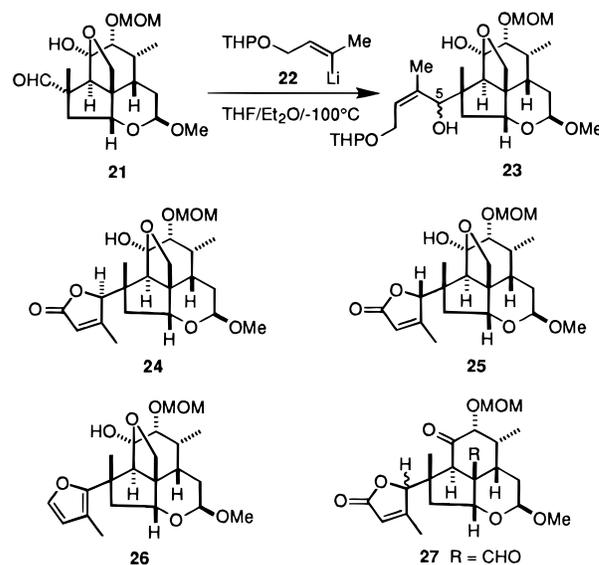
With pure crystalline **24** available, the protected lactol was hydrolyzed [60% aqueous HOAc, reflux, 20 min] and the resulting lactol was oxidized [Ag₂CO₃, Celite, benzene, reflux 1.5 h] giving rise (80%) to the corresponding δ-lactone which upon exposure to boron tribromide in methylene chloride at −45 °C gave rise (78%) to crystalline racemic 5(S)-polyandrane (**2**), mp 215−217 °C, whose spectral properties were found to be identical with those of an authentic sample of natural **2**.[1] Similarly, exposure of pure **25** to aqueous acetic acid followed by sequential treatment with Fetizon's reagent and BBr₃ provided access to 5(R)-polyandrane (**1**), mp 236−237 °C. The spectral properties of racemic **1** were identical in all respects with those of an authentic sample of natural **1**.[1]

Supporting Information Available: ¹H and ¹³C NMR spectra for **1, 2, 7−10, 12, 13, 15−21, 24, 25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992791E

(11) Huang-Minlon, *J. Am. Chem. Soc*. **1946**, *68*, 2487. Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301.

(12) Cf.: Grieco, P. A.; Sham, H. L.; Inanaga, J.; Kim, H.; Tuthill, P. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1345.

(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(14) Vinyllithium reagent **22** was prepared from the known[15] (**Z**)-3-iodo-but-2-en-1-ol via tetrahydropyranylation [DHP, TsOH, CH₂Cl₂] followed by treatment with 2.0 equiv of *tert*-butyllithium [Et₂O, −100 °C].[16]

(15) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949.

(16) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V. *Tetrahedron Lett.* **1978**, 1031.

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

(18) Fetizon, M.; Golfier, M. *Compt. Rend. (C)* **1968**, *267*, 900. Chakraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1984**, *25*, 2891.