Synthetic Studies on Quassinoids: Total Synthesis of Simalikalactone D and Assignment of the Absolute Configuration of the α-Methylbutyrate Ester Side Chain

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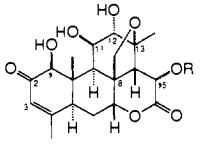
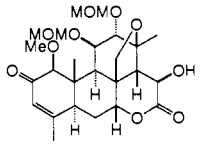
Simalikalactone D (**1**)[3] and quassimarin (**2**)[4] have occupied the attention of synthetic chemists for well over 15 years, in part because these cytotoxic substances exhibit potent activity in vivo against the P-388 lymphocytic leukemia in mice (PS). Attempts at total synthesis of **1** and **2** have been unsuccessful to date,[5,6] in part because development of a synthetic protocol for elaborating the highly oxygenated pentacyclic carbon ring system has proven to be a formidable challenge and, to a lesser extent, because the absolute configuration of the butyrate esters attached at C(15) has never been established.[7] The recent finding that quassinoids such as **1** and **2** possess marked differential solid tumor selectivity[8] prompts us to report the first total synthesis of simalikalactone D. Detailed below is the synthesis of pre-simalikalactone D (**3**), which permits the syntheses of the four possible diastereomers of **1** and the identification of one of these stereoisomers as simalikalactone D, the major constituent of *Quassia africana* Baill.



1, R = $COCH(CH_3)C_2H_5$
2, R = $COC(OAc)(CH_3)C_2H_5$



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(1) Abbott Predoctoral Fellow, 1991-1992.
(2) J. Stewart and Dagmar K. Riley Graduate Fellow, 1991-1992.
(3) Tresca, J.-P.; Alais, L.; Polonsky, J. *C. R. Seances Acad. Sci., Ser. C* **1971**, *273*, 601.
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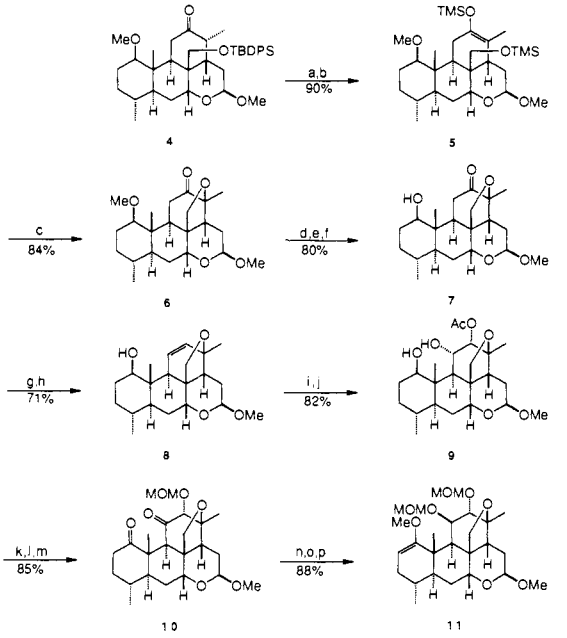
(6) For approaches to the construction of the C(8),C(13) epoxymethano bridge of quassinoids, see: (a) Kanai, K.; Zelle, R. E.; Sham, H.-L.; Grieco, P. A.; Callant, P. *J. Org. Chem.* **1984**, *49*, 3867. (b) Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (c) Kraus, G. A.; Taschner, M. J. *Ibid.* **1980**, *45*, 1175. (d) Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353. (e) Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686.
(7) The absolute configuration of the picrasane carbocyclic framework of the quassinoids follows from biosynthetic considerations [Connolly, J. D.; Overton, K. H.; Polonsky, J. The Chemistry and Biochemistry of the Limonoids and Quassinoids. In *Progress in Phytochemistry 2*; Reinhold, L., Liwschitz, Y., Eds.; Interscience: London, 1970; p 385], X-ray crystallographic data [Polonsky, J. *Proc. Chem. Soc.* **1964**, 292; Brown, W. A.; Sim, G. A. *Ibid.* **1964**, 293], and total synthesis [Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504.]
(8) Personal communication from Drs. Thomas H. Corbett and Frederick A. Valeriote, Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI.

Scheme I. Synthesis of the Fully Functionalized Ring C Pentacyclic Intermediate **11**[a]



[a] (a) TBAF (4.0 equiv), THF, 20 h. (b) TMSI (4.0 equiv), Et_3N (5.6 equiv), HMDS (5.6 equiv), $ClCH_2CH_2Cl$, -23 °C, 2.75 h. (c) NIS (1.1 equiv), THF, -78 °C, 1.3 h; TBAF (2.0 equiv), -78 → 0 °C, 1.75 h. (d) 10% HCl/THF (1:1), 20 h. (e) $AlCl_3$ (25 equiv), NaI (25 equiv), CH_3CN/CH_2Cl_2 (2:1), 2.5 h. (f) MeOH, concentrated HCl, THF, 1.5 h. (g) $TsNHNH_2$ (3.0 equiv), $MgSO_4$ (10 equiv), TsOH, THF, 17 h. (h) MeLi (15 equiv), THF, 0 °C (1 h) → room temperature (3 h). (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, -23 → 0 °C. (j) OsO_4 (1.4 equiv), pyridine, 17 h; $NaHSO_3$ (10 equiv), H_2O, pyridine, 27 h. (k) CrO_3 (10 equiv), pyridine (20 equiv), Celite, CH_2Cl_2, 0 °C → room temperature (4.25 h). (l) K_2CO_3, MeOH, 0 °C (30 min) → room temperature (1.5 h). (m) MOMCl (20 equiv), *i*-Pr_2NEt (24 equiv), $ClCH_2CH_2Cl$, 40 °C, 20 h. (n) LDA (5 equiv), HMPA (15 equiv), THF, -78 °C, 30 min; Me_2SO_4 (6.0 equiv), -78 °C (10 min) → 0 °C (40 min). (o) $LiAlH_4$ (5.0 equiv, 1.0 M in Et_2O), THF, 0 °C → room temperature (1.25 h). (p) MOMCl (20 equiv), *i*-Pr_2NEt (24 equiv), $ClCH_2CH_2Cl$, 45 °C, 11 h.

The synthesis of simalikalactone D commences with the known tetracyclic compound **4**[9] (Scheme I), wherein the ring C keto function serves as a vehicle for elaboration of (a) the C(8),C(13) epoxymethano bridge and (b) the C(11),C(12) trans diaxial vicinal diol unit. Initial attempts to transform (140 °C, DMF) the C(13) bromo ketone derived from **4** directly into pentacyclic ketone **6** possessing the epoxymethano bridge met with no success.[6a] However, cleavage of the *tert*-butyldiphenylsilyl ether followed by thermodynamic silyl enol ether formation provided **5**, which upon exposure to *N*-iodosuccinimide in tetrahydrofuran at -78 °C and subsequent treatment with tetra-*n*-butylammonium fluoride afforded **6**, mp 163.0-164.5 °C, in 76% overall yield from **4**. Prior to elaboration of the C(11),C(12) trans diaxial diol, the C(1) methyl ether was cleaved. The best results were obtained by hydrolyzing the protected lactol prior to cleavage of the methyl ether. After reprotection of the lactol, the resulting pentacyclic keto alcohol **7**, mp 213.5-215.5 °C, was transformed into the corresponding tosylhydrazone, which was treated with excess methyllithium to give rise to olefin **8**, mp 172.5-174.5 °C. Acetylation of **8** followed by exposure to osmium tetraoxide gave rise to diol acetate **9**, mp 244-245 °C, wherein the acetyl group of the C(1) acetate migrated exclusively to the less encumbered C(12) axial hydroxyl group. Before inversion of the configuration of the carbon bearing the hydroxyl group at C(11), diol **9** was oxidized, the corresponding diketo acetate was hydrolyzed, and

(9) Gross, R. S.; Grieco, P. A.; Collins, J. L. *J. Am. Chem. Soc.* **1990**, *112*, 9436.

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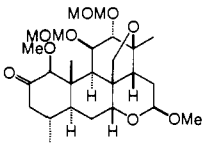
the resulting C(12) hydroxyl was reprotected as a methoxymethyl ether, giving rise to **10**, mp 159–160 °C, in 85% overall yield. Selective formation of the Δ^1 methyl enol ether and reduction of the C(11) keto function followed by protection of the resultant alcohol as a methoxymethyl ether provided **11**.

With the stereochemical features of ring C in place, attention was focused on introduction of a keto function at C(2) and a hydroxyl group at C(15). Hydroboration of the methyl enol ether in **11** and subsequent oxidation [PCC (3.0 equiv), NaOAc (2.5 equiv), CH_2Cl_2, Celite, 0 °C → room temperature] provided crystalline **12**, mp 205.5–207.0 °C, in 91% overall yield. Selective



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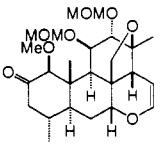

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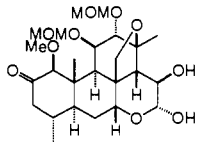
hydrolysis (5% HCl/THF, 1:1, 0 °C → room temperature) of the protected lactol followed by treatment with methanesulfonyl chloride (1.5 equiv) in methylene chloride containing triethylamine generated the sensitive dihydropyran **13**, which was treated directly with osmium tetraoxide to give rise (82%) to **14** and **15** in a 3:2 ratio. Upon treatment of the mixture of **14** and **15** with excess



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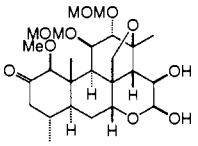

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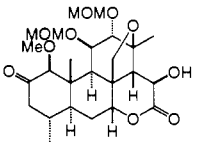
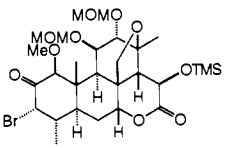


16

manganese dioxide in chloroform there was obtained a 54% yield of crystalline hydroxy lactone **16**, mp 224–225 °C, along with recovered (39%) lactol **15**.[10a] Exposure of **15** to 5% hydrochloric acid/tetrahydrofuran (1:2) gave rise (96%) to a 3:2 equilibrium mixture of **14** and **15**, which could be resubmitted to the manganese dioxide oxidation.[10b]

The synthesis of pre-simalikalactone D (**3**) was realized via a two-step sequence. Treatment of **16** with excess lithium hexamethyldisilazane in tetrahydrofuran at −78 °C followed by sequential addition of chlorotrimethylsilane (−78 → 0 °C) and *N*-bromosuccinimide (0 °C) provided crystalline bromo ketone **17**, mp 216–217 °C, in 93% yield. Much to our surprise, exposure of **17** to 1.5 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0 °C → room temperature) provided a 92% yield of pre-simalikalactone D (**3**), mp 209.5–211.0 °C.



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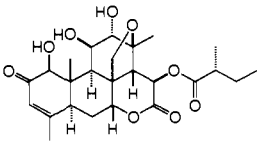
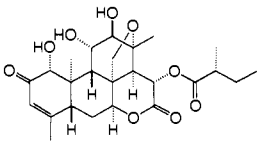
Completion of the synthesis of simalikalactone D necessitated determination of the absolute configuration of the α-methylbutyrate ester group attached at C(15). Toward this end, (±)-**3** was treated with (*R*)-2-methylbutyric anhydride[11] [Et_3N (4.0 equiv), DMAP (1.5 equiv), CH_2Cl_2, 5 h] to give rise to a 92% yield of two diastereomers, which were deprotected [1. $AlCl_3$ (15 equiv), NaI (15 equiv), CH_3CN/CH_2Cl_2 (2:1), 0 °C, 25 min; 2. BBr_3 (15 equiv), CH_2Cl_2, −45 °C, 45 min] in ca. 70% overall yield,



18



19

providing two diastereomers **18** and **19** which were readily separated by HPLC.[12,13] Synthetic (+)-**18** was found to be identical (mp, mmp, $[\alpha]_D$, IR, HPLC, ^1H NMR, ^{13}C NMR) with a sample of natural (+)-simalikalactone D kindly provided by Dr. J. Polonsky.

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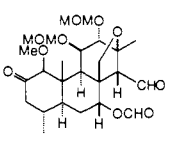
(10) (a) Stereoelectronic factors have been observed previously in the manganese dioxide oxidation of carbohydrate derivatives [Fraser-Reid, B.; Carthy, B. J.; Holder, N. L.; Yunker, M. *Can. J. Chem.* **1971**, *49*, 3038; also see Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 41–47]. (b) Use of Fetizon's reagent (Ag_2CO_3/Celite/benzene) in the oxidation of **14** and **15** led to substantial quantities of the C(15),C(16) cleavage product i, in addition to the desired hydroxy lactone **16**.



i

(11) (*R*)-2-Methylbutanoic acid, prepared according to the Evans protocol [Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737; Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141], was converted (DCC, CH_2Cl_2, 0 °C) into (*R*)-2-methylbutyric anhydride, bp 55 °C (0.1 mm), $[\alpha]^{25}_D$ −33.8° (*c* 0.014, CH_2Cl_2), in 91% yield.

(12) The HPLC separation was carried out on a Beckmann instrument (Model 101) using a preparative Chiracel OD column (10 mm i.d. × 50 cm) (mobile phase, absolute EtOH/hexane, 30:70 (v/v), flow rate, 4.2 mL/min, UV detection at 230 nm). The retention times of **18** ($[\alpha]^{25}_D$ +45.8° (*c* 0.006, dioxane)) [simalikalactone D ($[\alpha]^{25}_D$ +43.2° (*c* 0.006, dioxane))] and diastereomer **19** ($[\alpha]^{25}_D$ −63.7° (*c* 0.006, dioxane)) were 12.3 and 8.1 min, respectively.

(13) Initially, (±)-**3** was treated with commercially available (*S*)-2-methylbutyric anhydride (Et_3N, DMAP, CH_2Cl_2, 5 h), and the resulting mixture of C(15)-acylated compounds were deprotected [a. $AlCl_3$, NaI, CH_3CN/CH_2Cl_2 (2:1), 0 °C; b. BBr_3, CH_2Cl_2, −45 °C], giving rise to two diastereomers which were readily separated by HPLC (retention times 8.0 and 13.2 min), and shown not to be identical to simalikalactone D by coinjection with an authentic sample of **1**.

Silicon-Directed Aldol Condensation. Evidence for a Pseudorotational Mechanism

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Mechanistic studies of the reaction of the (*S*)-prolinol-derived *O*-silyl ketene *N,O*-acetal **1** with aromatic aldehydes are reported. Experiments with three *O*-silyl ketene *N,O*-acetals derived from different 1,2-amino alcohols are also described and lead to a coherent mechanistic picture involving pseudorotation of trigonal bipyramidal organosilicon intermediates.

Benzaldehyde and **1** react to form the (2*S*,3*R*)-anti aldol product **2** (77%) and traces of the (2*S*,3*S*)-syn product (2%).[1] The reaction proceeds readily at ambient temperature in solvents which are poor σ-donors (CH_2Cl_2, hexane, benzene, CH_3CN) but not at all in tetrahydrofuran or *N,N*-dimethylformamide, an observation suggestive of coordination of the aldehyde carbonyl

(1) Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672.

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