(*R*)-(+)- and (*S*)-(−)-5-Ethyl-5-methyl-1,3-dioxolane-2,4-dione Reagents for the Direct Preparation of α-Hydroxy-α-methylbutyrate Esters: Assignment of the Absolute Configuration of the α-Acetoxy-α-methylbutyrate Ester Side Chain of Quassimarin via Total Synthesis

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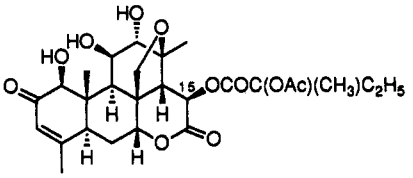
Summary: The preparation and use of (*R*)-(+)- and (*S*)-(−)-5-ethyl-5-methyl-1,3-dioxolane-2,4-diones for the direct preparation of chiral α-hydroxy-α-methylbutyrate esters are described.

Quassimarin (**1**),[3] like so many other complex quassinoids [e.g., glaucarubinone (**2**)[4]], has occupied the attention of synthetic and medicinal chemists for approximately 20 years because of the formidable challenge presented by its highly oxygenated pentacyclic carbon framework and the continuing studies which have clearly demonstrated that quassinoids[5] such as **1** and **2** possess marked differential solid tumor selectivity.[6] Attempts at the synthesis of quassimarin have been unsuccessful to date.[7] One of the obstacles to completion of a synthesis of **1** has been, in part, the fact that the absolute configuration of the α-acetoxy-α-methylbutyrate ester attached at C(15) was never established by Kupchan and Streelman[3] during their structure elucidation studies and, to a lesser extent, the fact that there are no general methods available for the direct preparation of α-hydroxy-α-methylbutyrate esters. We detail below the preparation and use of (*R*)-(+)- and (*S*)-(−)-5-ethyl-5-methyl-1,3-dioxolane-2,4-diones (**3**) and (**4**), respectively, for the direct preparation of α-hydroxy-α-methylbutyrate esters. Also detailed below is the acylation of (−)-pentacyclic alcohol **5** with **3** and **4** which permits the synthesis of two diastereomers of quassimarin,



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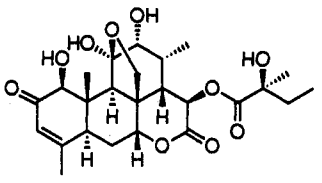

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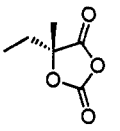

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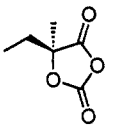

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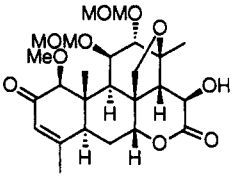

5

thus establishing the configuration of the derived α-hydroxy-α-methylbutyric acid as *R*.

Under the assumption that the acetylated α-hydroxy-α-methylbutyrate ester present in quassimarin was of the same absolute configuration as the α-hydroxy-α-methylbutyrate found in glaucarubinone (**2**), the known[8] (*S*)-(+)-2-hydroxy-2-methylbutyric acid (**6**)[9] was converted into **4** by treatment (reflux, 5 h) of **6** with 1.0 equiv of triethylamine and 0.67 equiv of triphosgene in tetrahydrofuran.[10] Workup provided, after distillation (bp 60–62 °C, 1 mmHg), a 70% yield of (*S*)-(−)-dioxolanedione **4**, $[\alpha]^{25}_{D}$ −26.6° (*c* 2.38, $CHCl_3$).

(1) Abbott Predoctoral Fellow, 1991–1993.
(2) J. Stewart and Dagmar K. Riley Graduate Fellow, 1991–1992.
(3) Kupchan, S. M.; Streelman, D. R. *J. Org. Chem.* **1976**, *41*, 3481.
(4) Gaudemer, A.; Polonsky, J. *Phytochemistry* **1965**, *4*, 149. Nyburg, S. C.; Walford, G. L.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1965**, 203.
(5) For reviews on quassinoids see: Kawada, K.; Kim, M.; Watt, D. S. *Org. Prep. Proc. Int.* **1989**, *21*, 521. Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 221.
(6) Unpublished results with Drs. Thomas H. Corbett and Frederick A. Valeriote, Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI.
(7) For model studies on quassimarin and closely related quassinoids, see: Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. Kraus, G. A.; Taschner, M. J. *Ibid.* **1980**, *45*, 1175. Kraus, G. A.; Taschner, M.; Shimagaki, M. *J. Org. Chem.* **1982**, *47*, 4271. Grieco, P. A.; Sham, H.-L.; Inanaga, J.; Kim, H.; Tuthill, P. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1345. Kanai, K.; Zelle, R. E.; Sham, H.-L.; Grieco, P. A.; Callant, P. *J. Org. Chem.* **1984**, *49*, 3867. Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353. McKittrick, B. A.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5897. Inanaga, J.; Sasaki, S.; Grieco, P. A.; Kim, H. *J. Am. Chem. Soc.* **1985**, *107*, 4800. Sasaki, S.; Grieco, P. A.; Huffman, J. C.; Callant, P.; Imamura, P. M. *J. Org. Chem.* **1985**, *50*, 4880. Schlessinger, R. H.; Wong, J.; Poss, M. A.; Setoi, H.; Takeno, H.; Hashimoto, M. *Ibid.* **1985**, *50*, 3950. Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1986**, *27*, 1339. Demir, A.; Gross, R. S.; Dunlap, N. K.; Bashir-Hashemi, A.; Watt, D. S. *Ibid.* **1986**, *27*, 5567. Kraus, G. A.; Krolski, M. E. *J. Org. Chem.* **1986**, *51*, 3347. Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Jaw, J. Y.; Tu, S. *Ibid.* **1987**, *52*, 3346. Grieco, P. A.; Inanaga, J.; Sham, H.-L.; Sasaki, S.; Kim, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1044. Spohn, R. F.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491. Shishido, K.; Takahashi, K.; Fukumoto, K.; Kametani, T.; Honda, T. *J. Org. Chem.* **1987**, *52*, 5704. Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *Ibid.* **1987**, *52*, 1686. Kim, M.; Gross, R. S.; Sevestre, H.; Dunlap, N.; Watt, D. S. *Ibid.* **1988**, *53*, 93. Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Heterocycles* **1988**, *27*, 495. Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504.
(8) Mattocks, A. R. *J. Chem. Soc.* **1964**, 1918.
(9) Hydroxy acids **6** and **7** were prepared according to the protocol of Koga: Jew, S.-s.; Terashima, S.; Koga, K. *Tetrahedron* **1979**, *35*, 2337.
(10) For the synthesis of 5-substituted 1,3-dioxolane-2,4-diones using trichloromethyl chloroformate see: Toyooka, K.; Takeuchi, Y.; Kubota, S. *Heterocycles* **1989**, *29*, 975.

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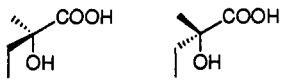
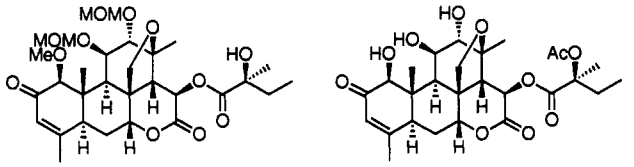


6 7

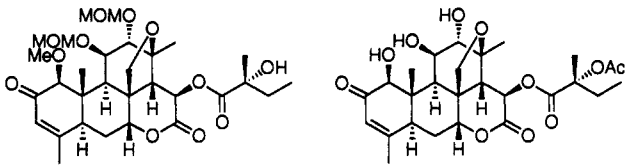
Exposure of a 0.06 M solution of pentacyclic alcohol 5[11] in methylene chloride containing 1.1 equiv of 4-(dimethylamino)pyridine to 2.5 equiv of 4 for 8.5 h at ambient temperature gave rise (75%) to pentacyclic α-hydroxy ester 8. Acetylation (Ac_2O, Et_3N, DMAP, CH_2Cl_2, 38.5 h) of 8



8 9

followed by removal of the protecting groups [(1) $AlCl_3$ (15 equiv), NaI (15 equiv), CH_3CN–CH_2Cl_2 (2:1), 0 °C, 30 min; (2) BBr_3 (15 equiv), CH_2Cl_2, −45 °C, 70 min] gave rise, in 69% overall yield, to pentacyclic compound 9 [mp 284–287 °C dec, $[\alpha]^{25}_D$ +30.7° (c 0.14, $CHCl_3$)] whose physical and spectral properties were different from those of natural quassimarin published in the literature.[3]

The above study thus establishes the structure of quassimarin as 11. The *R*-configuration of the C(15) side chain was unambiguously confirmed as detailed below by synthesis. Treatment of the known[8] (*R*)-(−)-2-hydroxy-2-methylbutyric acid (7)[9] with triphosgene under the identical conditions detailed above afforded after distillation (bp 58–60 °C, 1 mmHg) a 64% yield of 3, $[\alpha]^{25}_D$ +28.4° (c 1.29, $CHCl_3$). Treatment of a 0.06 M solution of 5 in methylene chloride with 3.5 equiv of dioxolanedione 3 and 1.6 equiv of 4-(dimethylamino)pyridine provided, after 25 h at ambient temperature, a 77% yield of 10,

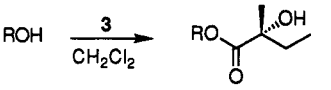


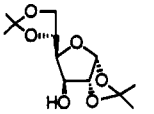
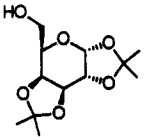
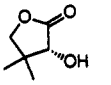
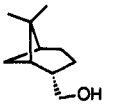
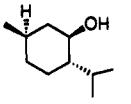
10 11

$[\alpha]^{25}_D$ −61.2° (c 0.93, $CHCl_3$). Upon acetylation [Ac_2O (10 equiv), Et_3N (20 equiv), DMAP, CH_2Cl_2, 21 h] and subsequent deprotection [(1) $AlCl_3$, NaI, CH_3CN–CH_2Cl_2 (2:1), 0 °C, 25 min; (2) BBr_3, CH_2Cl_2, −45 °C, 75 min] as detailed above, a 70% yield (overall) of crystalline (+)-quassimarin (11) [mp 240–241 °C, $[\alpha]^{25}_D$ +22.4° (c 0.25, $CHCl_3$) (lit.[3] mp 237.5–238.5 °C, $[\alpha]^{25}_D$ +22.4° (c 0.26, $CHCl_3$))] was obtained. The ^1H NMR spectrum of synthetic (+)-11 was identical to that of the natural material recorded in the literature.

(11) Prepared as described previously starting with (*R*)-(−)-8a-methyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenedione [Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764].

Table I. Preparation of (*R*)-α-Hydroxy-α-methylbutyrate Esters[a]



entry	substrate	equiv of 3	time, h	yield[b] (%)
1		1.5	5	80
2		1.5	1.5	84
3		1.3	1	85
4	cholestanol	2	6.5	80
5		1.3	1.5	77
6		1.5	5.5	90

[a] All reactions were conducted at ambient temperature employing a 0.1 M solution of substrate in methylene chloride containing 1.1 equiv of 4-(dimethylamino)pyridine. [b] Isolated yields.

The procedure detailed above for the preparation of chiral α-hydroxy-α-methylbutyrate esters employing 3 and 4 is applicable to a variety of alcohols including sterically encumbered alcohols. Illustrated in Table I are a number of substrates bearing hydroxyl groups which have been transformed into (*R*)-α-hydroxy-α-methylbutyrate esters. Reactions are typically conducted in methylene chloride at ambient temperature employing 1.3–2.0 equiv of 3 and 1.1 equiv of 4-(dimethylamino)pyridine. Reactions are complete in 1–6.5 h and yields are in the range of 77–90%. The above methodology should be generally applicable to a wide range of α-hydroxy-α-substituted alkanoate esters employing appropriately substituted 1,3-dioxolane-2,4-diones.

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Supplementary Material Available: Procedures and compound characterization data (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.