Pergamon

Tetrahedron Letters, Vol. 35, No. 40, pp. 7401-7404, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01524-4

Model Study and Partial Synthesis of Prehispanolone and 14,15-Dihydroprehispanolone from Hispanolone[1]

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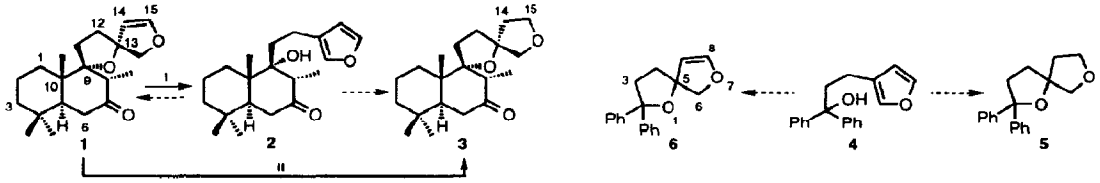
Abstract: Employing an intramolecular Michael addition as a pivotal step, furan **4** has been converted to dioxaspiro compounds **5** and **6**, whose heterocyclic frameworks constitute important structural units of 14,15-dihydroprehispanolone **3** and prehispanolone **1**, respectively. Hispanolone **2** was converted to **3** as well as **1** by utilizing a similar strategy.

We recently reported that hispanolone **2** was obtained through a mild acid hydrolysis of prehispanolone **1**,[3,4] which was a specific platelet activating factor (PAF) receptor antagonist.[5,6] Catalytic hydrogenation of **1** converted it to the bioactive and acid-insensitive 14,15-dihydroprehispanolone **3**.[3,4,6] For further pharmacological evaluation purpose, it appears that both **1** and **3** are good leads for a structure-activity relationship study.

Scheme 1.



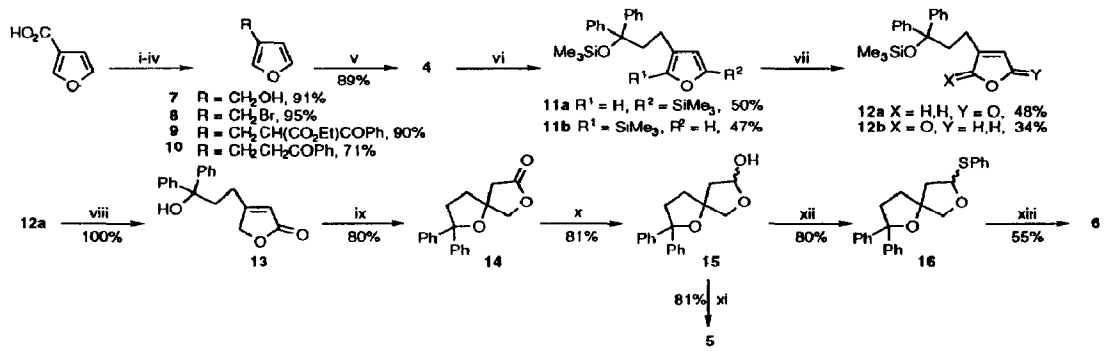
i, 0.5% HCl, EtOAc, (100%); ii, H_2, 5% Pd-C, EtOAc, (91%)

In view of its relative structural simplicity, furan **2** could serve as a key intermediate *en route* to the total synthesis of **1** and **3**. For assessment reason, nevertheless, we also initiated a program to construct three model compounds, namely **5**, **6** and **4**. Here we report the synthesis of **5** and **6** from **4**, as well as the construction of **1** and **3** from **2**.

To our best knowledge, no arduous attempt to construct dioxaspiro[4,4]nonene framework[7] similar to that of **1** has been recorded, notwithstanding that such spiro moiety is a common structural unit in many natural products.[4,8] As outlined in Scheme 2, the synthesis of **4** from 3-furoic acid was straightforward.[9] The deprotonation-silylation of furan **4**,[10] gave **11a** and **11b** in 1:1 ratio. Peracid oxidation[11] of a mixture of **11a**

and **11b** afforded the chromatographically separable **12a** and **12b**. Desilylaion of **12a** furnished **13**.[12] An intramolecular Michael addition of **13** gave **14**.[13] which was reduced[14,15] via **15** to give **5**. On the other hand, phenyl sulfide **16** was prepared and subsequent oxidation and elimination[16] eventually yielded **6**.

Scheme 2.



i, $LiAlH_4$, Et_2O; ii, PPh_3, CBr_4, CH_2Cl_2, 0°C; iii, NaH, $PhCOCH_2CO_2Et$, THF, 0°C; iv, 5% NaOH, then 2N HCl; v, PhLi, Et_2O, -78°C; vi, 2.2 equiv *n*-BuLi, TMEDA, Et_2O, 0°C, then 2.5 equiv Me_3SiCl, THF, 0°C; vii, $MeCO_3H$, NaOAc, CH_2Cl_2, 7°C; viii, 2N HCl; ix, K_2CO_3, MeOH; x, *i*-Bu_2AlH, CH_2Cl_2, -78°C; xi, Et_3SiH, CF_3CO_2H, CH_2Cl_2, -78°C; xii, PhSH, CF_3CO_2H, CH_2Cl_2, 0→25°C; xiii, MCPBA, CH_2Cl_2, 0°C, then $(EtO)_3P$, PhMe, heat

Similar routes were utilized to construct **1** and **3** from the readily available **2**.[3] As shown in Scheme 3, protection of the keto group of **2** gave **17**. Deprotonation and silylation of **17** yielded a mixture of **18a** and **18b**, which was not separated and was oxidized with peracid to furnish a chromatographically separable mixture of butenolides **19a** and **19b**. Desilylation of **19a** converted it to the key intermediate **20**, which underwent an intramolecular Michael addition to give again a chromatographically separable mixture of a pair of diastereomers **21a** and **21b**, the only stereochemical difference being the 13*S* or 13*R* configuration, respectively. It is significant to note that the biosynthetic pathway leading to the absolute configuration of the spiro carbon (C-13) in **1** is probably non-enantiospecific, because two related compounds, namely scutellone B and scutellone G have been identified.[17]

The 13*S* configuration of **21a** was established by its DIBAL reduction, from which both **22** and a crystalline side product **23** were isolated. The X-ray crystallographic analysis of **23**[18] unequivocally certified its 13*S* configuration and further revealed that the molecular conformation is stabilized by intramolecular hydrogen bonding involving both hydroxyl groups, one of which acting as a donor in the bifurcated mode (Figure 1). Further conversion (deprotection and silane reduction) of **22** led to the "non-natural" **24**,[19] whose spiro carbon C-13 must be also of *S* configuration.

In principle, the verification of the 13*S* configuration of **21a** also indirectly substantiated the

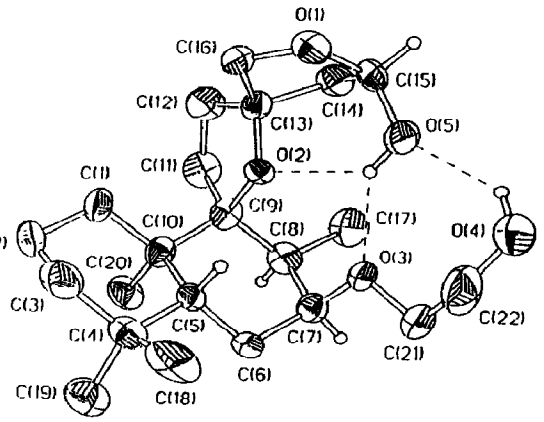
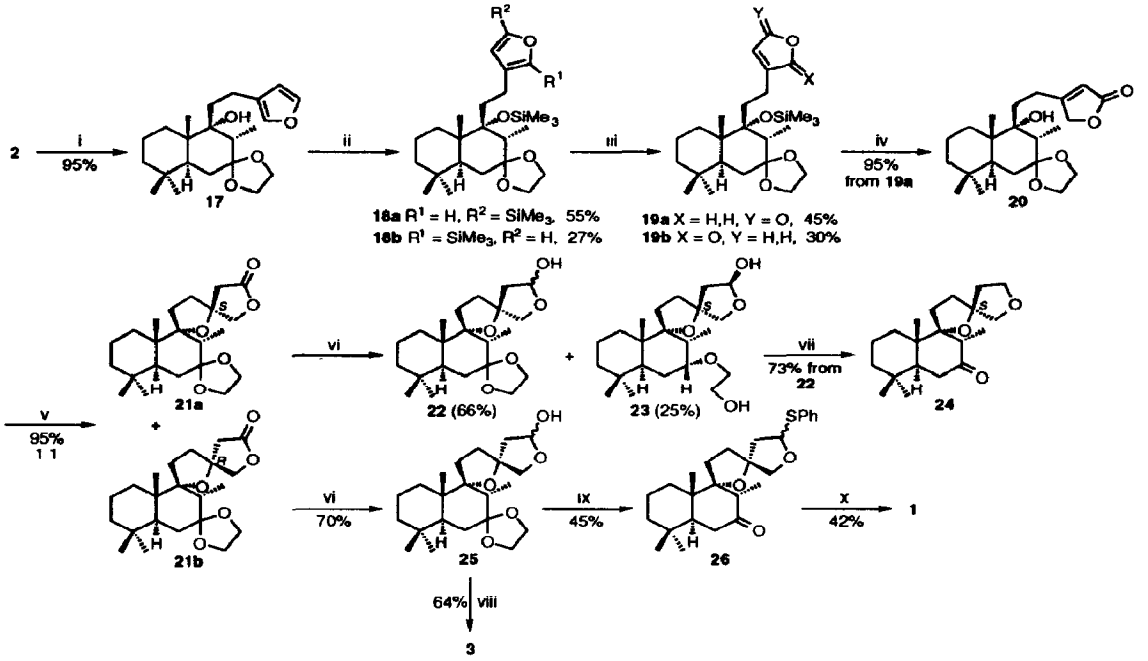


Figure 1. X-ray single crystal structure of **23**.

13*R* configuration of **21b**, which was likewise reduced to **25**. Compound **3**[19] was obtained upon silane reduction and concomitant deprotection. The physical and spectroscopic properties of **3** were identical with those of a "natural" **3** obtained through catalytic hydrogenation of the natural **1**.[3] However, it was necessary to apply a modified Ley procedure[16] to convert **25** to **1**, presumbly due to the interference of the C-7 keto group regenerated during the conversion of **25** to **26**. Thermal elimination of **26** eventually gave **1**,[19] whose physical and spectroscopic data were identical to those of the natural **1**.[3]

Scheme 3.



i, $(CH_2OH)_2$, *p*-TsOH, C_6H_6, heat; ii, 2.2 equiv *n*-BuLi, C_6H_{14}, TMEDA, 0°C, then 2.5 equiv Me_3SiCl, Et_2O, 0°C, iii, $MeCO_3H$, NaOAc, CH_2Cl_2, 7°C; iv, BF_3•Et_2O, CH_2Cl_2, -10°C, v, DBN-Et_3N; vi, *i*-Bu_2AlH, CH_2Cl_2, -78°C, vii, 3 equiv CF_3CO_2H, CH_2Cl_2, -78→ -25°C, then Et_3SiH, BF_3•Et_2O, CH_2Cl_2, -78→25°C; viii, Et_3SiH, BF_3•Et_2O, CH_2Cl_2, -78→25°C, ix, PhSH, CF_3CO_2H, CH_2Cl_2, 0→25°C; x, 0.5 M $NaIO_4$, MeOH, 0→25°C, then $(EtO)_3P$, PhMe, heat

Acknowledgement: This work is supported by a Hong Kong Research Grants Council Earmarked Grant (Acc. No. 221300230). E.S.W. was on leave from Jilin University, China and B.S.L. from Wuhan University, China on a Croucher Fellowship.

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18. *Crystal data* for **23** (Siemens P4 system using Mo-K_α radiation, λ = 0.71073 Å): $C_{22}H_{38}O_5$, M = 382.52, colorless orthorhombic prism, space group $P2_12_12_1$ (No. 19), a = 10.370(2), b = 11.785(2), c = 17.454(3)Ä, ρ_{calc} = 1.191 g cm^{-3}, Z = 4, $F(000)$ = 840, crystal size 0.20 x 0.42 x 0.60 mm. The structure was refined using SHELXTL-PLUS[20] for 1436 observed reflections [$2\theta_{max}$ = 50°, $|F_o| > 3\sigma(|F_o|)$] and 242 variables to R_F = 0.056 and R_{wF2} = 0.080 with the weighting scheme $w = [\sigma^2(|F_o|) + 0.0013|F_o|^2]^{-1}$ and an extinction parameter χ = 0.0016(5) where $F_c^* = F_c[1 + 0.002\chi F_c^2/\sin 2\theta]^{-1/4}$. Tables of atomic parameters have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, United Kingdom.
19. Selected physical and spectroscopic data : Compounds **1**: oil; $[\alpha]_D^{25}$ -64.6° (C_6H_6, *c* 0.85) [lit[1] $[\alpha]_D^{22}$ -63.6° (C_6H_6, *c* 0.55)]. Compound **3**: oil; $[\alpha]_D^{27}$ -32.2° ($CHCl_3$, *c* 0.72) [lit[1] $[\alpha]_D^{22}$ -33.6° ($CHCl_3$, *c* 0.60)]. Compound **20**: solid; m.p. 140-141°C; $[\alpha]_D^{25}$ 10.90° ($CDCl_3$; *c* 5.0). Compound **21a**: oil; $[\alpha]_D^{24}$ 20.6° ($CDCl_3$; *c* 4.35). Compound **21b**: oil; $[\alpha]_D^{24}$ -14.3° ($CDCl_3$; *c* 4.60). Compound **24**: oil; $[\alpha]_D^{27}$ -111° ($CHCl_3$, *c* 0.18); ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 6H), 1.06 (d, *J* 6.5 Hz, 3H), 1.12 (s, 3H), 1.20-1.31 (m, 3H), 1.42-1.59 (m, 3H), 1.85-1.93 (m, 3H), 1.97-2.04 (m, 2H), 2.15-2.30 (m, 3H), 2.35-2.49 (m, 1H), 2.72 (q, *J* 6.5 Hz, 1H), 3.51-3.68 (ABq, *J* 8.4 Hz, 2H), 3.79-3.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 8.74, 17.21, 18.13, 20.73, 29.10, 29.29, 32.12, 33.18, 37.63, 38.64, 39.76, 41.18, 42.36, 46.47, 50.01, 66.92, 77.32, 90.65, 95.94, 210.20.
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(*Received in Japan* 27 *May* 1994)