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First Synthesis of (+)-Brazilane from (+)-Brazilin

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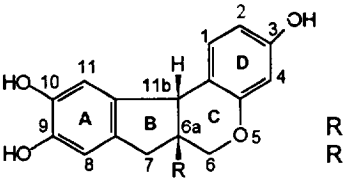
Abstract: The first synthesis of the enantiomerically pure brazilane was achieved from brazilin by the radical deoxygenation reaction of tertiary alcohols which took place with retention of configuration.

Brazilane **1** is one of the synthetic derivatives of brazilin **2**, a member of the homoflavonoid family isolated from the heartwood of *Caesalpinia sappan*[1]. The racemic brazilane has already been mentioned as a crude mixture. However, its purification and characterization have never been effected[2,3]. Racemic O-trimethylbrazilane has been obtained either by total synthesis[4, 5] or by hemisynthesis from brazilin[2,6]. To our knowledge, the enantiomerically pure brazilane has never been synthesized. As part of our study directed towards the development of a new tool for the measurement of superoxide dismutase (SOD) activity[7], it was decided to prepare brazilane **1**. In this communication, we report for the first time the synthesis of the enantiomerically pure brazilane **1** by deoxygenation of brazilin **2**.

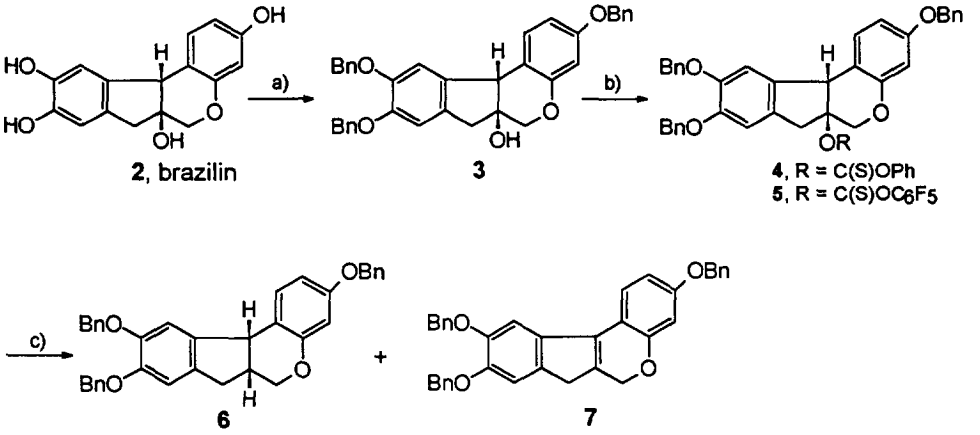


R = H, Brazilane
R = OH, Brazilin **2**

Brazilin **2** bears two adjacent asymetric carbons in the junction of the BC rings. The aim of our synthesis was to carry out a deoxygenation of the tertiary alcohol while preserving the chirality. Due to this constraint, all classical methods generating a sp^2 carbon in the intermediate could not be used here. Some other methods[8], such as the dissolving metals reduction of ester derivatives of alcohol[9], the photolysis of acetates[10] and the stannane reduction of various ester derivatives[11] could be used under these circumstances. We have chosen to study the radical deoxygenation approach.

The three phenoxyl groups of brazilin **1** were protected as tribenzylbrazilin **3** according to Dann et al.[12] (Scheme 1). Robins' modification[13] of Barton and McCombie's deoxygenation reaction[14] was first applied to this tertiary alcohol. Thus, compound **3** was deprotonated with MeLi at -70 °C and treated with phenyl chlorothionoformate to give **4**[15] in 97% yield. When the compound **4** was heated with 1.5 eq. of Bu_3SnH under reflux in benzene for 30 mn in the presence of a catalytic amount of AIBN, brazilane derivative **6** was isolated in 84% yield together with a very small amount of the elimination product **7**. The absence of AIBN afforded the

elimination compound as major product. The thionocarbonate **4** was thermally unstable and a Chugaev-type elimination took place. Thus, heating **4** alone in toluene under reflux for 1.5 h produced **7** in 84% yield. It is noteworthy that this reductive deoxygenation is generally used in secondary alcohols[13] and fails with the tertiary ones[8,11].

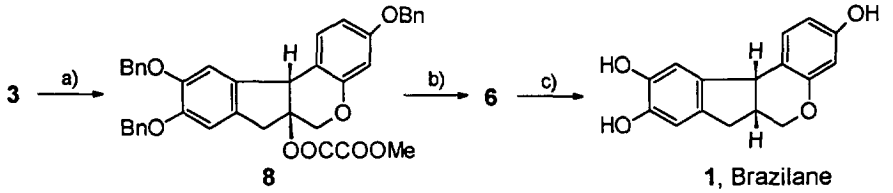


Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux, 18 h, 85%; (b) for **4**: (i) MeLi, THF, -70°C to rt; (ii) ClC(S)OPh, -70°C to rt, 97%; for **5**: (i) MeLi, THF, -70°C to rt; (ii) ClC(S)OC_6F_5, -70°C to rt, 64%; (c) from **4**: Bu_3SnH, AIBN (cat.), benzene, reflux, 0.5 h, 84%; from **5**: *idem*, 71%.

Scheme 1

Several other reactions were examined and gave less satisfactory results. Pentafluorophenylthionocarbonate[16] **5** produced, under the same conditions as that for **4**, tribenzylbrazilane **6** in 71% yield with a small amount of the starting alcohol **3** and the alkene **7** (Scheme 1). On the other hand, the deoxygenation reaction through the corresponding thiohydroxamate[17] failed. When the crude chloride prepared from alcohol **3** and oxalyl chloride was added to a mixture of the salt of 2-mercaptopyridine-N-oxide and tertBuSH in benzene under reflux, only the corresponding thioxalate (16%) and the starting alcohol **3** were obtained after treatment.

The procedure described by Dolan et al.[18] with the reduction of methyl oxalate was also found useful for our purpose (Scheme 2). Direct treatment of **3** with methyl oxalyl chloride at reflux in THF gave **8** along with some decomposition products. Methyl oxalate **8** was preferably prepared (90%) by deprotonation with MeLi and treatment with methyl oxalyl chloride. Treatment of compound **8** with 1.5 eq. Bu_3SnH in the presence of AIBN (cat.) (reflux in toluene, 20 mn) afforded the alkane **6** in 71% yield. No trace of the elimination product **7** was found.

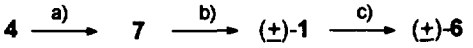


Reagents and conditions: (a) (i) MeLi, THF, -70°C to rt; (ii) ClC(O)COOMe, -70°C to rt, 90%; (b) Bu_3SnH, AIBN (cat.), toluene, reflux, 20 mn, 71%; (c) H_2, 10% Pd/C, AcOEt, rt, 18 h, 100%.

Scheme 2

Tribenzylbrazilane **6** ($[\alpha]^{25}_D$ +2 (c 1.02, CH_2Cl_2)) obtained from **4**, **5** and **8** showed a coupling constant of 7.9 Hz between H-6a and H-11b indicating a *cis* junction between rings B and C. This was further proved by

comparison with racemate (±)-**6** prepared by the catalytic hydrogenation of the alkene **7** and the tribenzylation of the resulting racemic brazilane (±)-**1** whose *cis* structure was unequivocal (Scheme 3). From the fact that the chirality of C-11b was not affected during the radical deoxygenation and that the BC rings were of *cis* junction, we deduced that the configuration of C-6a was retained.



Reagents and conditions: (a) toluene, reflux, 1.5 h, 84%; (b) H_2, 10% Pd/C, AcOEt, rt, 18 h, 100%; (c) BnBr, K_2CO_3, acetone, reflux, 18 h, 96%.

Scheme 3

In the above deoxygenation reactions, no trace of the *trans* analog was formed. From a mechanistic point of view, the radical deoxygenation of **4**, **5** and **8** occurs probably *via* a configurationally favoured sp^3 radical, resulting in the retention of the starting configuration. Configuration inversion would entail a planar radical intermediate which would be energetically unfavourable due to the ring constraint.

Finally, the catalytic hydrogenation of tribenzylbrazilane **6** (10% Pd/C, H_2, AcOEt) afforded quantitatively brazilane **1**: $[\alpha]^{25}_D$ +103 (c 1.00, MeOH) (Scheme 2).

In conclusion, we have described the first hemisynthesis of enantiomerically pure brazilane **1**. The radical deoxygenation mediated by Bu_3SnH in the presence of a catalytic amount of AIBN was particularly efficient for the tertiary alcohol derivatives **4**, **5** and **8** and took place with retention of configuration. The use of a phenylthionocarbonate derivative allowed to work under mild conditions and gave the best results.

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15. All new compounds gave satisfactory analytical and spectroscopic data.
Selected data: **1**: mp 157-159°C; $[\alpha]^{25}_D$ +103 (c 1.00, MeOH); ^{1}H NMR (acetone-d_6): δ = 2.37 (dd, 1 H, J = 2.3, 15.4 Hz, H-7), 2.69 (m, 1 H, H-6a), 2.92 (dd, 1 H, J = 7.3, 15.4 Hz, H-7'), 3.38 (t, 1 H, J = 10.2 Hz, H-6), 3.93 (dd, 1 H, J = 4.5, 10.2 Hz, H-6'), 3.98 (d, 1 H, J = 7.9 Hz, H-11b), 6.17 (d, 1 H, J = 2.4

Hz, H-4), 6.37 (dd, 1 H, J = 2.4, 8.3 Hz, H-2), 6.58 (s, 1 H, H-8), 6.71 (s, 1 H, H-11), 7.10 (d, 1 H, J = 8.3 Hz, H-1), 7.42 (s, 1 H, OH exchangeable with D_2O), 7.48 (s, 1 H, OH exchangeable with D_2O), 8.02 (s, 1 H, OH exchangeable with D_2O).

4: mp: 101-103°C; $[\alpha]^{25}_D$ +23 (c 0.97, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ = 3.05 (d of AB system, 1 H, J = 16.6 Hz, H-7), 3.71 (d of AB system, 1 H, J = 16.6 Hz, H-7'), 3.73 (d, 1 H, J = 12.7 Hz, H-6), 4.59 (s, 1 H, H-11b), 5.05 (s, 2 H, $C\underline{H}_2Ph$), 5.06 (AB system, 2 H, J = 12.0 Hz, $C\underline{H}_2Ph$), 5.10 (s, 2 H, $C\underline{H}_2Ph$), 5.28 (dd, 1 H, J = 1.8, 12.7 Hz, H-6'), 6.56 (d, 1 H, J = 2.5 Hz, H-4), 6.71 (dd, 1 H, J = 2.5, 8.5 Hz, H-2), 6.78 (s, 1 H, H-8), 6.88(s, 1 H, H-11), 7.05 (m, 2 H, H_{arom}), 7.19 (d, 1 H, J = 8.5 Hz, H-1), 7.28-7.46 (m, 18 H, H_{arom}).

5: mp 62-64°C; $[\alpha]^{25}_D$ -9 (c 0.51, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ = 3.48 (d of AB system, 1 H, J = 15.8 Hz, H-7), 3.68 (d of AB system, 1 H, J = 15.8 Hz, H-7'), 3.75 (d, 1 H, J = 12.7 Hz, H-6), 4.60 (s, 1H, H-11b), 5.04 (s, 2 H, $C\underline{H}_2Ph$), 5.06 (AB system, 2 H, J = 11.7 Hz, $C\underline{H}_2Ph$), 5.10 (s, 2 H, $C\underline{H}_2Ph$), 5.20 (dd, 1 H, J = 1.3, 11.7 Hz, H-6'), 6.57 (d, 1 H, J = 2.5 Hz, H-4), 6.73 (dd, 1 H, J = 2.5, 8.5 Hz, H-2), 6.78 (s, 1 H, H-8), 6.88(s, 1 H, H-11), 7.21 (d, 1 H, J = 8.5 Hz, H-1), 7.25-7.50 (m, 15 H, H_{arom}).

6: mp 113-115°C; $[\alpha]^{25}_D$ +2 (c 1.02, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ = 2.56 (dd, 1 H, J = 2.3, 15.6 Hz, H-7), 2.80-2.88 (m, 1 H, H-6a), 3.10 (dd, 1 H, J = 7.2, 15.6 Hz, H-7'), 3.62 (dd, 1 H, J = 9.9, 10.7 Hz, H-6), 4.08 (dd, 1 H, J = 4.4, 10.7 Hz, H-6'), 4.16 (d, 1 H, J = 6.9 Hz, H-11b), 5.02 (s, 2 H, $C\underline{H}_2Ph$), 5.10 (s, 4 H, 2 $C\underline{H}_2Ph$), 6.49 (d, 1 H, J = 2.6 Hz, H-4), 6.64 (dd, 1 H, J = 2.6, 8.4 Hz, H-2), 6.82 (s, 1 H, H-8), 6.95 (s, 1 H, H-11), 7.17 (d, 1 H, J = 8.4 Hz, H-1), 7.30-7.50 (m, 15 H, H_{arom}).

7: mp: 141°C (decomposition); ^1H NMR ($CDCl_3$): δ = 3.30 (s, 2 H, H-7), 5.06 (s, 2 H, $C\underline{H}_2Ph$), 5.02 (s, 2 H, H-6), 5.17 (s, 2 H, $C\underline{H}_2Ph$), 5.20 (s, 2 H, $C\underline{H}_2Ph$), 6.59 (s, 1 H, H-8), 6.61 (dd, J = 2.6, 7.2 Hz, 1 H, H-2), 7.11 (s, 1 H, H-11), 7.29 - 7.52 (m, 17 H, H_{arom}).

8: $[\alpha]^{25}_D$ +36 (c 0.79, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ = 3.37 (AB system, 2 H, J = 16.8 Hz, H-7), 3.74 (d, 1 H, J = 12.5 Hz, H-6), 3.83 (s, 3 H, $OC\underline{H}_3$), 4.49 (s, 1 H, H-11b), 4.73 (dd, 1 H, J = 1.3, 12.5 Hz, H-6'), 5.03 (s, 2 H, $C\underline{H}_2Ph$), 5.07 (AB system, 2 H, J = 11.7 Hz, $C\underline{H}_2Ph$), 5.10 (s, 2 H, $C\underline{H}_2Ph$), 6.52 (d, 1 H, J = 2.6 Hz, H-4), 6.71 (dd, 1 H, J = 2.6, 8.5 Hz, H-2), 6.78 (s, 1 H, H-8), 6.88 (s, 1 H, H-11), 7.15-7.50 (m, 16 H, H-1 and H_{arom}).

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