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Synthesis of the tetracyclic core of the bisabosquals

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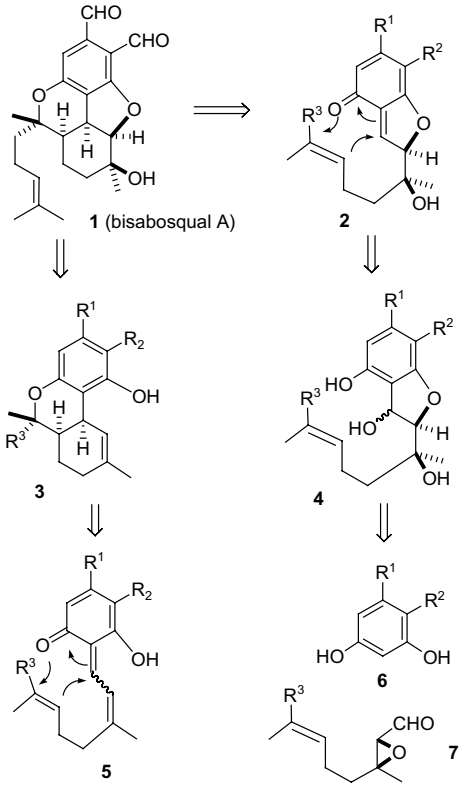
Abstract—HCl-catalyzed deprotection and cyclization of **8b** provided tricycle **9b** cleanly. Epoxidation of **9b** afforded tetracycle **13** with the wrong stereochemistry at the tertiary alcohol. Selective elimination of the tertiary alcohol to give the exocyclic methylene compound, alkene cleavage to form the ketone with OsO_4 and $NaIO_4$, and addition of MeMgBr to the ketone from the least hindered face gave tertiary alcohol **16** with the tetracyclic core of bisabosqual A (**1**).

Bisabosqual A (**1**) was isolated in 2001 from the culture broth of *Stachybotrys* sp. RF-7260, obtained from decaying tree leaves.[1] Three related natural products, bisabosquals B–D, were isolated from *Stachybotrys ruwenzoriensis* RF-6853. Bisabosqual A (**1**) inhibits the microsomal squalene syntheses from *Saccharomyces cerevisiae*, *Candida albicans*, HepG2 cell, and rat liver with IC_{50} values of 0.43, 0.25, 0.95, and 2.5 μg/mL, respectively, and has broad antifungal activities against various yeasts. This activity suggests that bisabosqual A might be useful for treatment of hypercholesterolemia.

The novel tetracyclic structure of bisabosqual A (**1**) was determined by 2D NMR experiments and confirmed by X-ray crystallography of bisabosqual B.[2] The three six-membered rings of **1** are analogous to those of tetrahydrocannabinols (THCs), although the cyclohexane and pyran rings are *trans*-fused in the extensively investigated THCs[3] and *cis*-fused in **1**. The additional furan ring and tertiary alcohol of **1** pose additional synthetic challenges.

Initially, we thought that the tetracycle of bisabosqual A might be accessible by an inverse electron demand hetero Diels–Alder reaction of quinone methide **2**.[4] The furan ring of **2** will force the Diels–Alder reaction to give the desired *cis*-ring fusion (see Scheme 1). Quinone methide **2** could be formed by dehydration of dihydrobenzofuranol **4**, which would be prepared from resorcinol **6** and epoxyaldehyde **7**. Although we were able to prepare **4**, R^1, $R^2 = H$, CHO, $R^3 = Me$, all



Scheme 1. Retrosynthetic analysis of bisabosqual A (**1**).

Keywords: Quinone methide; Inverse electron demand Diels–Alder reaction; Alcohol inversion.
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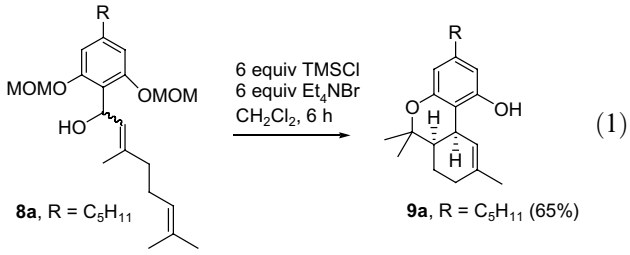
attempts to generate quinone methide **2** resulted in dehydration to form the benzofuran.[5]

We therefore considered methods for the preparation of bisabosqual A (**1**) by oxidative cyclization of *cis*-fused tricycle **3**, which can be prepared by inverse electron demand Diels–Alder reaction of quinone methide **5**. Although hexahydrocannabinoids are invariably formed with a *trans*-ring fusion, Rickards found that treatment of **8a** with TMSCl and Et_4NBr cleaved the MOM ethers and generated a quinone methide that cyclized to give 65% of the *cis*-fused tetrahydrocannabinoid tricycle **9a** (see Eq. 1).[6]



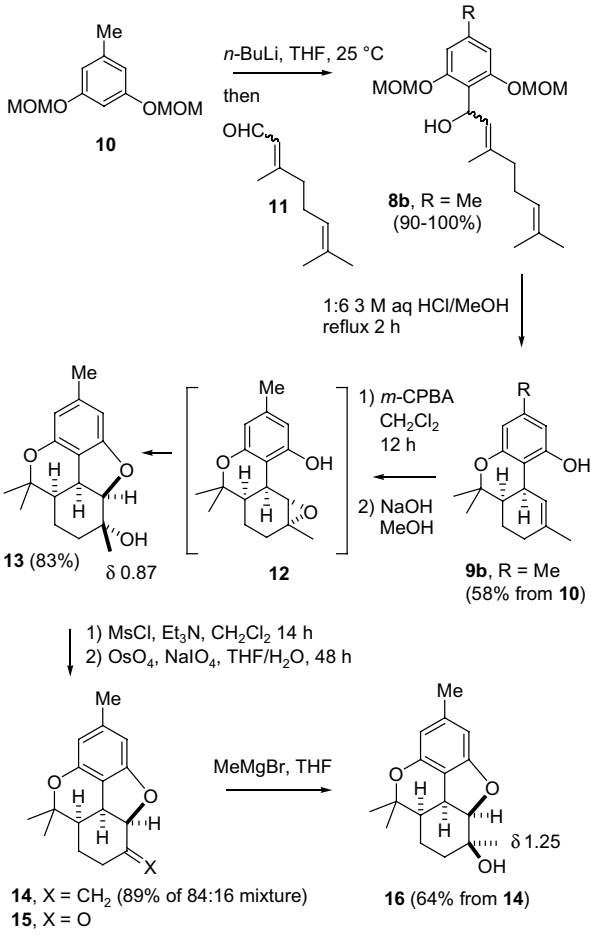
(1)

Deprotonation at the 2-position of the bis MOM ether of orcinol (**10**)[7] with *n*-BuLi in THF followed by addition of citral (**11**) afforded 90–100% of **8b** as a ≈60:40 *E*:*Z* mixture that decomposed on chromatography (see Scheme 2). In our hands, treatment of crude **8b** with TMSBr,[8] TMSCl and Et_4NBr, or TMSCl and Bu_4NBr in CH_2Cl_2 at 25 °C gave no **9b**. Use of TMSBr at −78 °C provided 60% of the MOM ether of **9b** (not shown), which can also be obtained in 70% yield with TMSCl and NaI at −20 °C.[9] After extensive experimentation, we found that complete deprotection of **8b** and cyclization to **9b** can be effected in 58% overall yield from **10** by heating **8b** in a 1:6 mixture of 3 M aqueous hydrochloric acid and MeOH at reflux for 2 h. Tricycle **9b**[10] is somewhat unstable and can only be purified on MeOH-deactivated silica gel.

syn-Oxidative cyclization[11,12] of **9b** would yield the desired tertiary alcohol **16** in a single step. Not surprisingly, treatment of **9b** with $(CF_3CO_2)ReO_3$, $(Cl_2HCCO_2)ReO_3$, or PCC led to complex mixtures of products. All previous oxidative cyclizations have started with unsaturated alcohols, rather than phenols. The electron rich phenol should be more easily oxidized than the alkene. This reactivity order was also observed during attempted iodocyclization. Treatment of **9b** with bis(collidine)iodonium hexafluorophosphate[13] afforded the diiodo phenol.

Finally, we decided to epoxidize **9b** from the less hindered α-face with *m*-CPBA in CH_2Cl_2 as reported by Razdan and co-workers in a similar system.[14] The initially formed epoxy phenol **12** partially cyclized to give tetracycle **13**[15] with the desired ring system, but the wrong stereochemistry at the tertiary alcohol. Treatment of this mixture with methanolic NaOH for 2 h provided 83% of **13**.

The rigidity of the ring system allowed us to develop an efficient procedure to convert **13** to the desired alcohol



Scheme 2. Synthesis of tetracyclic core **16**.

16. Treatment of **13** with MsCl and excess Et_3N in CH_2Cl_2 provided 89% of an 84:16 mixture of **14**[16] and the endocyclic isomer. Formation of the less stable alkene **14** is favored because only the methyl protons can adopt the required antiperiplanar orientation to the equatorial leaving group (see Fig. 1). Oxidative cleavage of the alkene mixture with OsO_4 and $NaIO_4$ gave ketone **15**.[17] Addition of MeMgBr to the ketone in THF occurred selectively from the less hindered α-face (see Fig. 1) to afford the desired tertiary alcohol **16**[18] in 64% yield from **14**.

The spectral data of the cyclohexanol protons and carbons of **16** correspond closely to those of bisabosqual A (**1**), while those of **13** are quite different. In particular,

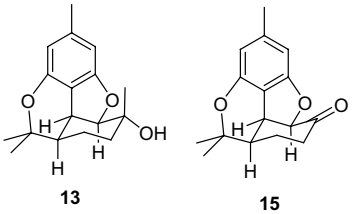


Figure 1. 3-Dimensional structures of **13** and **15**.

MeCOH absorbs at δ 1.25 in **16** and δ 1.26 in **1**, but at δ 0.87 in the epimeric alcohol **13**.

In conclusion, we have developed a short and efficient route to the tetracyclic core of the bisabosquals. We are currently extending the sequence to more highly functionalized resorcinols and farnesal, rather than citral, as needed for the synthesis of bisabosqual A.

Acknowledgements

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10. Preparation of **9b**: A 3 M solution of HCl (22 mL, 65 mmol) was added to a solution of **8b** (2.0 g, 5.49 mmol) in MeOH (130 mL). The reaction was heated at reflux for 2 h, cooled to 25 °C, quenched with saturated $NaHCO_3$, and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 1.48 g (104%) of crude **9b**. Flash chromatography of the residue on MeOH-deactivated silica gel (hexanes) gave 825 mg (58%) of tricycle **9b** that was 90–95% pure: ^{1}H NMR 6.24 (s, 1), 6.22 (br s, 1), 6.12 (s, 1), 4.92 (br s, OH), 3.58–3.53 (br, 1), 2.18 (s, 3), 2.00–1.89 (m, 3), 1.74–1.66 (m, 1), 1.68 (s, 3), 1.52–1.42 (m, 1), 1.39 (s, 3), 1.27 (s, 3); ^{13}C NMR 154.8, 153.8, 137.3, 135.0, 121.8, 110.7, 109.3, 108.7, 76.2, 40.0, 31.4, 29.7, 25.9, 25.2, 23.7, 20.9, 20.6; HRMS (DEI) calcd for $C_{17}H_{22}O_2$ (M^+) 258.1620, found 258.1612.
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15. Preparation of **13**: A solution of *m*-CPBA (276 mg, 1.357 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of **9b** (254 mg, 0.984 mmol) in CH_2Cl_2 (54 mL) at 0 °C. The reaction was stirred for 12 h at 25 °C and concentrated. The orange residue was taken up in Et_2O, which was washed with Na_2SO_3, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was taken up in MeOH (40 mL) and 4% NaOH (25.1 mL) was added to the solution. The reaction was stirred at 25 °C for 2 h. The MeOH was evaporated and the aqueous phase was extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on MeOH-deactivated silica gel (hexanes) gave 224 mg (83%) of **13**: ^{1}H NMR 6.19 (s, 1), 6.16 (s, 1), 4.85 (br d, 1, $J = 8.6$), 3.72 (dd, 1, $J = 8.6$, 6.7), 2.26 (s, 3), 1.97 (ddd, 1, $J = 11.6$, 6.7, 6.1), 1.74–1.65 (m, 2), 1.48–1.36 (m, 1), 1.41 (s, 3), 1.34 (s, 3), 0.96 (dddd, 1, $J = 14.3$, 11.0, 11.0, 4.3), 0.87 (s, 3); ^{13}C NMR 161.2, 151.9, 140.4, 107.57, 107.51, 102.4, 93.6, 79.0, 73.2, 37.6, 35.2, 34.8, 26.7, 26.0, 24.6, 22.1, 19.3; HRMS (DEI) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1558.
16. Preparation of **14**: MsCl (0.8 mL, 10.2 mmol) was added dropwise to a solution of **13** (157 mg, 0.573 mmol) and Et_3N (2.7 mL, 18.8 mmol) in CH_2Cl_2 (23 mL) at 0 °C. The reaction was stirred for 14 h at 25 °C, quenched with 2 M HCl, and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on MeOH-deactivated silica gel (hexanes) gave 130 mg (89%) of an 84:16 mixture of **14** and the endocyclic isomer: ^{1}H NMR (**14**) 6.25 (s, 1), 6.16 (s, 1), 5.33 (br d, 1, $J = 7.9$), 5.14 (br s, 1), 4.81 (br s, 1), 3.68 (br dd, 1, $J = 7.9$, 7), 2.27 (s, 3), 2.24 (ddd, 1, $J = 12$, 3, 3), 2.00 (ddd, 1, $J = 12$, 6, 6), 1.88–1.75 (m, 2), 1.40 (s, 3), 1.34 (s, 3), 0.92–0.82 (m, 1); (partial data for endocyclic isomer) 5.50 (br d, 1, $J = 5.2$), 5.20 (br d, 1, $J = 8$), 3.77–3.72 (m, 1), 2.25 (s, 3); ^{13}C NMR 160.4, 151.9, 144.8, 140.0, 110.3, 107.7, 106.7, 103.3, 86.6, 78.7, 39.7, 36.5, 31.8, 26.4, 26.2, 23.7, 22.2; HRMS (DEI) calcd for $C_{17}H_{20}O_2$ (M^+) 256.1463, found 256.1471.
17. Preparation of **15**: OsO_4 (42 μL of a 2.5% solution in *t*-BuOH, 0.004 mmol) and $NaIO_4$ (53 mg, 0.246 mmol) were added to a solution of **14** (21 mg, 0.082 mmol) in THF–H_2O (2:1, 1 mL). The reaction was stirred at 25 °C for 48 h and concentrated. The residue was taken up in H_2O and extracted with EtOAc. The combined extracts were washed with $Na_2S_2O_3$ and brine, and dried ($MgSO_4$). Flash chromatography of the residue on MeOH-deactivated silica gel (9/1 hexane–EtOAc) gave 19 mg (92%) of 80% pure ketone **15**: ^{1}H NMR 6.36 (s, 1), 6.18 (s, 1), 5.05 (d, 1, $J = 7.9$), 4.07 (br dd, 1, $J = 7.9$, 7), 2.41–2.20 (m, 2), 2.26 (s, 3), 1.9–1.6 (m, 2), 1.46 (s, 3), 1.40 (s, 3), 0.9–0.8 (m, 1); ^{13}C NMR 208.4, 160.5, 151.4, 141.1, 108.4, 103.4, 87.5, 78.5, 39.1, 38.7, 29.7, 26.7, 26.4, 22.7, 22.1 (one quaternary carbon was not observed).
18. Preparation of **16**: MeMgBr (0.21 mL, 0.214 mmol) was added to a solution of partially purified ketone **15** (14 mg, 0.054 mmol) in THF (1 mL) at 0 °C. The reaction was stirred for 1 h at 25 °C, quenched with NH_4Cl, and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on MeOH-deactivated silica gel

(hexanes) gave 10.4 mg (70%) of **16**: ^{1}H NMR 6.22 (s, 1), 6.17 (s, 1), 4.70 (br d, 1, $J = 8.5$), 3.66 (br dd, 1, $J = 8.5, 6$), 2.26 (s, 3), 1.84 (ddd, 1, $J = 11.6, 6, 6$), 1.71 (br d, 1, $J = 11.6$), 1.60–1.40 (m, 1), 1.42 (s, 3), 1.33 (s, 3), 1.25 (s, 3), 1.26–1.16 (m, 2); ^{13}C NMR 161.4, 151.6, 140.3, 108.1, 107.6, 101.4, 90.5, 78.8, 69.4, 38.6, 34.9, 34.1, 29.6, 26.7, 26.1, 22.2, 16.5; HRMS (DEI) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1570.