ORGANIC LETTERS

2007
Vol. 9, No. 14
2705−2708

Reconciling Icetexane Biosynthetic Connections with Their Chemical Synthesis: Total Synthesis of (±)-5,6-Dihydro-6α-hydroxysalviasperanol, (±)-Brussonol, and (±)-Abrotanone

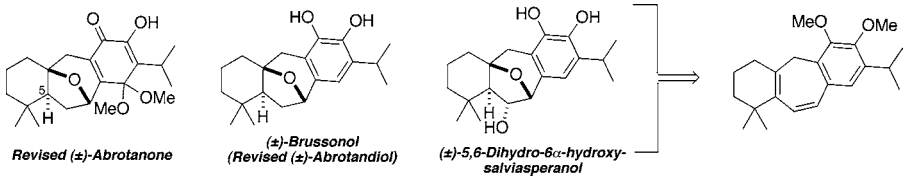
Eric M. Simmons, Jennifer R. Yen, and Richmond Sarpong*

Department of Chemistry, University of California, Berkeley, California 94720

rsarpong@berkeley.edu

Received May 29, 2007

ABSTRACT



A unified strategy for the chemical synthesis of the icetexane diterpenoids brussonol and 5,6-dihydro-6α-hydroxysalviasperanol has led to a structural revision of the recently isolated natural products abrotandiol and abrotanone.

The icetexane family of natural products encompasses a variety of structurally unique and bioactive compounds (Figure 1). Congeners include salviasperanol (**1**) and 5,6-dihydro-6α-hydroxysalviasperanol (**2**), which are found in the roots of *Salvia aspera*.[1] The reduction (hydrogenation) product of salviasperanol, named brussonol (**3**), was isolated from the roots of *Salvia broussonetii* and displays moderate cytotoxicity toward both insect and mammalian cell lines.[2] The related compound demethylsalvicanol (**4**) has been isolated from a number of sources including *Coleus barbatus*,[3] *Salvia mellifera*,[4] and more recently *Perovskia abrotanoides*.[5] Brussonol (**3**) and demethylsalvicanol (**4**) show cytotoxic activity against P388 murine leukemia cells, with IC_{50} values of 1.9 and 0.71 μg/mL, respectively.[6] In addition, dimers of these compounds such as grandione (**5**), which was isolated from the evergreen tree *Torreya grandis*,[7] have been reported.

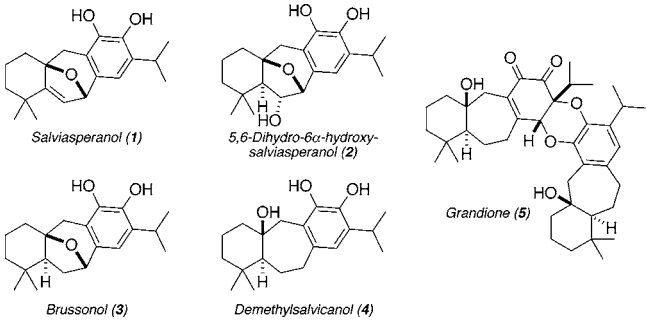


Figure 1. Icetexane diterpenoids.

(1) Esquivel, B.; Flores, M.; Hernandez-Ortega, S.; Toscano, R. A.; Ramamoorthy, T. P. *Phytochemistry* **1995**, *39*, 139−143.

(2) Fraga, B. M.; Diaz, C. E.; Guadano, A.; Gonzalez-Coloma, A. *J. Agric. Food Chem.* **2005**, *53*, 5200−5206.

(3) Kelecom, A.; Medeiros, W. L. B. *Bull. Soc. Chim. Belg.* **1989**, *98*, 413−414.

(4) Gonzalez, A. G.; Andres, L. S.; Luis, J. G.; Brito, I.; Rodriguez, M. L. *Phytochemistry* **1991**, *30*, 4067−4070.

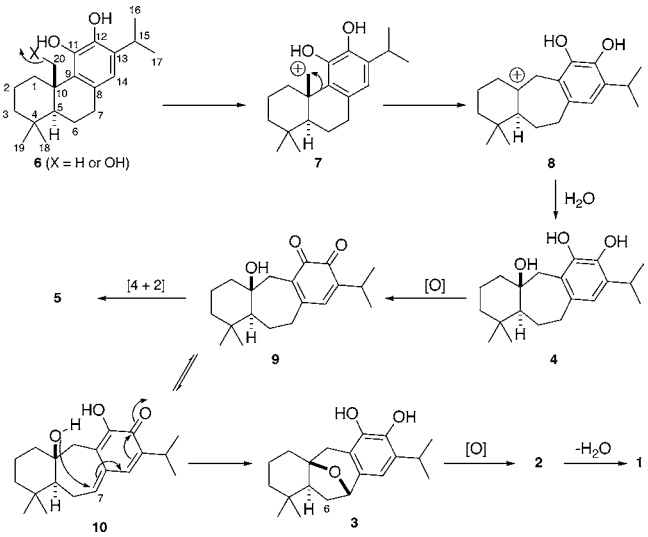
(5) Aoyagi, Y.; Takahashi, Y.; Satake, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Shiina, T.; Kurihara, T. *Tetrahedron Lett.* **2005**, *46*, 7885−7887.

(6) Aoyagi, Y.; Takahashi, Y.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S.; Kurihara, T. *Chem. Pharm. Bull.* **2006**, *54*, 1602−1604.

10.1021/ol0712428 CCC: $37.00
Published on Web 06/09/2007

The structural similarity of these natural products points to a probable biosynthetic connection via a series of reduction or oxidation events. It is likely that the abietane [6-6-6] tricyclic skeleton (**6**, Scheme 1) serves as the biosynthetic precursor to the icetexanes via a ring-expanding rearrangement.[2,4]

Scheme 1. Potential Biosynthesis of the Icetexanes

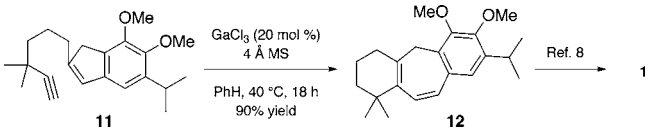


From the abietane core, loss of hydride (or hydroxide) from C20 and migration of the C9−C10 bond (which may be either concerted or stepwise via the intermediacy of **7**) would lead to carbocation **8**, which upon trapping with water would yield demethylsalvicanol (**4**).[4] Oxidation of the catechol moiety of **4** provides quinone **9**, which would yield grandione (**5**) following hetero-Diels−Alder dimerization. Notably, the latter sequence (**4** → **5**) has been successfully reproduced in a laboratory setting by Takeya and co-workers by using a sample of naturally isolated demethylsalvicanol (**4**).[5] Alternatively, tautomerization of **9** to give **10**, followed by intramolecular conjugate addition of the C10 hydroxyl to the electrophilic *p*-quinone methide carbon (C7) would yield brussonol (**3**).[2,6] Finally, brussonol may be converted to 5,6-dihydro-6α-hydroxysalviasperanol (**2**) by oxygenation at C6. Subsequent dehydration gives rise to salviasperanol (**1**).[2]

Our interest in this class of natural products stems primarily from the intricate biosynthetic connections between these interesting structures as well as their varied biological activity. We recently reported the total synthesis of (±)-salviasperanol (**1**) from benzannulated cycloheptadiene **12** (Scheme 2), which was prepared from alkynyl indene **11** by using a $GaCl_3$-catalyzed cycloisomerization reaction.[8]

Following this initial work, we turned our attention to the synthesis of the other members of this family of diterpenoids.

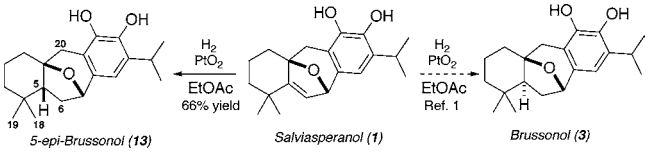
Scheme 2. Cycloisomerization Strategy to Salviasperanol (**1**)



Cognizant of the strong biosynthetic links between the congeners of this natural product class, we focused on 5,6-dihydro-6α-hydroxysalviasperanol (**2**) and brussonol (**3**) as our next targets given their close structural relationship to salviasperanol (**1**). During the course of our synthetic studies, we became aware of several inconsistencies in the literature with regard to the assigned structures of several of the icetexane natural products. Presented herein is our analysis of these discrepancies, as well as our synthetic efforts that we believe now resolve these incongruities.

We began our studies by examining a possible direct conversion of salviasperanol (**1**) to brussonol (**3**). In the initial 1995 account on the isolation of **1**, it was reported that hydrogenation with PtO_2 as a catalyst (Scheme 3) led to **3**.[1]

Scheme 3. Hydrogenation of Salviasperanol (**1**)



At the time, **3** was not a known natural product, but in 2005 it was isolated from natural sources and named brussonol.[2] Our comparison of the ^{1}H NMR spectral data reported for the hydrogenation product of **1** with that reported for naturally isolated **3** reveals several important differences. For example, while chemical shifts of δ 0.93 and 0.91 ppm were reported for the C18 and C19 methyl groups of the hydrogenation product of **1**, corresponding values for brussonol (**3**) were given as δ 0.93 and 0.82 ppm. Even greater disparity is found in a comparison of the resonances for the methylene protons at C20, which were reported as δ 2.71 and 2.37 ppm (J = 16 Hz) for **3**, whereas the corresponding resonances in the hydrogenation product appear at δ 3.16 and 2.69 ppm (J = 17.6 Hz). In addition, examination of the X-ray crystal structure of **1**,[1] and computer-generated molecular models (Figure 2), reveals a high degree of concavity of the central seven-membered ring. This should preclude approach from the α-face by the reducing agent and favor β-approach. The combination of these considerations led us to infer that 5-*epi*-brussonol (**13**), and not brussonol (**3**), had been obtained upon hydrogenation of salviasperanol (**1**). This was supported by our independent hydrogenation of **1**, which gave a product with ^{1}H NMR data identical with that previously reported. As expected, both ^{1}H and ^{13}C NMR data for our hydrogenation product were inconsistent with that given for **3**, confirming that hydrogenation of **1** yields 5-*epi*-brussonol (**13**) and not brussonol (**3**).

(7) Galli, B.; Gasparrini, F.; Lanzotti, V.; Misiti, D.; Riccio, R.; Villani, C.; Guan-Fu, H.; Zhong-Wu, M.; Wan-Fen, Y. *Tetrahedron* **1999**, *55*, 11385−11394.

(8) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883−2886.

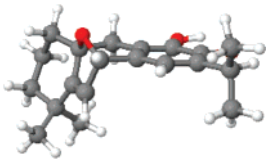
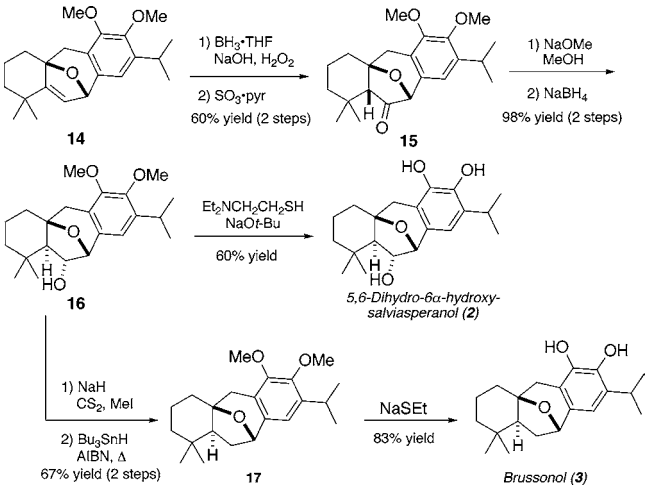


Figure 2. Energy-minimized representation of **1**.[9]

While an opportunity for a direct comparison of the spectral data obtained for the hydrogenation product of **1** (i.e., **13**) and brussonol (**3**) was not possible prior to the isolation of **3**, the inconsistencies in the icetexane literature were perpetuated by another report. Specifically, the isolation of 5,6-dihydrosalviasperanol (i.e., brussonol, **3**) was described in 1999,[10] and it was noted that the ^{1}H NMR data (while not reported) are "identical to [that] published for the synthetic substance obtained from the catalytic hydrogenation of salviasperanol [i.e., **13**]".[10] However, our analysis of the ^{13}C NMR data reported for 5,6-dihydrosalviasperanol is consistent with that obtained for brussonol (**3**) and not 5-*epi*-brussonol (**13**).

To conclusively settle the matter, we sought to synthesize **3** and compare its spectral data with that previously obtained for 5,6-dihydrosalviasperanol and brussonol. We reasoned that oxygenation at C6 of **13** (Scheme 3) would allow for epimerization of the neighboring C5 hydrogen to yield the more thermodynamically stable *trans* ring fusion, as well as provide access to 5,6-dihydro-6α-hydroxysalviasperanol (**2**). To that end, hydroboration of **14** (Scheme 4), which was

Scheme 4. Synthesis of 5,6-Dihydro-6α-hydroxysalviasperanol (**2**) and Brussonol (**3**)



readily available from our synthesis of salviasperanol,[8] followed by two-stage oxidation gave ketone **15** in 60% yield (over two steps). In line with our prediction, treatment of **15** with base led to complete isomerization to the *trans*-fused 6,7-bicycle, which upon $NaBH_4$ reduction gave alcohol **16** in 98% yield (over two steps). Cleavage of the methyl ethers by using a modification of the conditions reported by Magano and co-workers[11] gave synthetic 5,6-dihydro-6α-hydroxy-salviasperanol (**2**) in 60% yield, which gave spectral data in agreement with that reported following its isolation from natural sources.[1] Alternatively, subjecting **16** to Barton deoxygenation conditions[12] gave **17** in 67% yield (over two steps). Cleavage of the methyl ethers afforded **3** in 83% yield. Synthetic **3** gave spectral data identical with those reported for 5,6-dihydrosalviasperanol,[10] as well as to those reported for brussonol,[2] confirming the structure of **3** and establishing the equivalence of 5,6-dihydrosalviasperanol and brussonol.

Recently, a report on the isolation of two new icetexane diterpenoids from *Perovskia abrotanoides* appeared in the literature.[13] The structures proposed for abrotandiol and abrotanone, **18** and **19**, respectively, are shown in Figure 3.

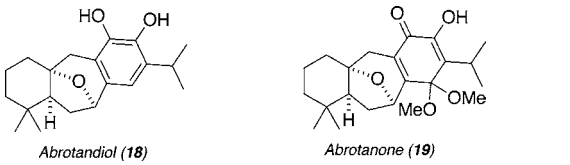


Figure 3. Proposed structures of abrotandiol and abrotanone.[13]

Inspection of **18** reveals that it is identical with 5-*epi*-brussonol (**13**), though illustrated as the antipode. On the basis of our conclusions regarding the stereochemical assignment of the other icetexane diterpenoids, we were prompted to carry out an analysis of **18** and **19**.

First, we recognized that the ^{1}H and ^{13}C NMR data provided for **18** matched exactly those which had been obtained for naturally occurring 5,6-dihydrosalviasperanol/brussonol (**3**),[2,10] as well as synthetic **3**, but were inconsistent with the data for **13**.[14] Second, the isolation of demethylsalvicanol (**4**, Scheme 1) from *Perovskia abrotanoides*, the same species that yields **18** and **19**, has been reported previously.[5] Given that brussonol (**3**) is likely a biosynthetic derivative of **4**, it seems highly unlikely that an organism that produces **4** would produce *epi*-brussonol (i.e., abrotandiol, **18**) instead of brussonol (**3**).

We propose that the correct structure of abrotandiol is **3**, making it identical with 5,6-dihydrosalviasperanol/brussonol. Accordingly, the structure of abrotanone (**19**), which is most likely derived from abrotandiol, should also be revised. To unambiguously establish the correct structure of abrotanone, we sought to prepare it from brussonol/abrotandiol (**3**).

(9) Energy minimization (MM2) performed with Chem3D Pro Version 8.0.

(10) Luis, J. G.; Andres, L. S. *Nat. Prod. Lett.* **1999**, *14*, 25−30.

(11) Magano, J.; Chen, M. H.; Clark, J. D.; Nussbaumer, T. *J. Org. Chem.* **2006**, *71*, 7103−7105.

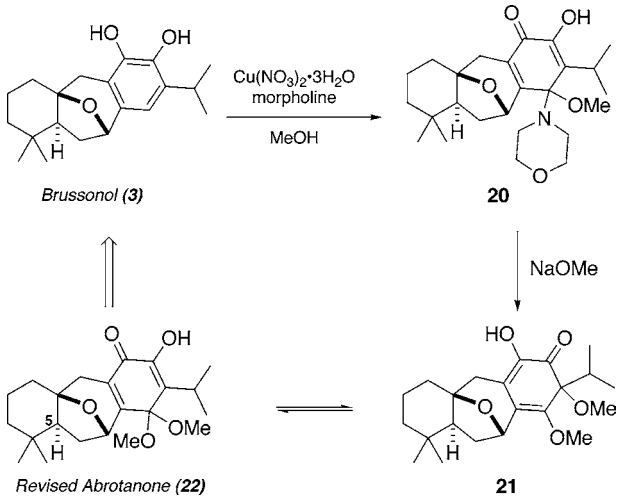
(12) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

(13) Khaliq, S.; Volk, F.-J.; Frahm, A. W. *Planta Med.* **2007**, *73*, 77−83.

(14) For details, see the Supporting Information.

Formally, this process involves a net four-electron oxidation of **3** with concomitant regioselective addition of 2 equiv of methanol. Perusal of the literature revealed only a handful of examples of such a transformation. Of these, we were drawn to a report by Löwer and co-workers that suggested this process could be mediated by Cu^{2+}.[15] In the event, treatment of **3** with $Cu(NO_3)_2 \cdot 3H_2O$ and morpholine in MeOH led to formation of hemiaminal **20** (Scheme 5).

Scheme 5. Synthesis of the Revised Structure of Abrotanone (**22**)



Subjecting **20** to NaOMe in MeOH gave a 2:1 equilibrium mixture of isomeric α-hydroxydieneones **21** and **22**, which were separable by column chromatography.[16] The dimethylketal **22** gave spectral data consistent with those reported for abrotanone. On the basis of this finding, it is evident that the structure of abrotanone is **22** and not **19** and must be revised accordingly.

Further evidence for our structural revision of abrotanone (see **22**) was provided by our synthesis of the intially proposed structure (**19**) from 5-*epi*-brussonol (**13**) by a sequence analogous to that shown in Scheme 5. Spectral data for **19** were *not* consistent with the data reported for abrotanone.[14]

With regard to the absolute configuration of the icetexanes, it has been determined by X-ray crystallography for a sample of demethylsalvicanol (**4**) that was isolated from *Perovskia abrotanoides* to be 5*S*,10*S*.[5] Given that abrotandiol and abrotanone (revised to **3** and **22**, respectively) were isolated from the same plant species, it is likely that the absolute configuration of abrotanone (**22**) is also 5*S*,10*S*. However, it should be noted that an optical rotation of −36.9 was reported for brussonol (**3**),[2] while a value of +20.2 was given for abrotandiol (revised to **3** in this work).[13] Since NMR data as well as biosynthetic considerations strongly suggest that these compounds are identical, this discrepancy in optical rotation merits further investigation, which is currently ongoing.[17]

In conclusion, we report the synthesis of 5,6-dihydro-6α-hydroxysalviasperanol (**2**) and 5,6-dihydrosalviasperanol/brussonol (**3**) from salviasperanol dimethyl ether. In the course of our studies, we have determined that hydrogenation of salviasperanol does not yield **3** as reported, but instead gives 5-*epi*-brussonol (**13**). In addition, we propose a structural revision of the recently reported natural products abrotandiol and abrotanone. Abrotandiol, which was proposed to have a structure identical to that of 5-*epi*-brussonol, is in fact identical to brussonol (**3**), while the configuration at C5 of abrotanone should be revised such that the 6,7-ring fusion is *trans* (see **22**). The proposed stereochemical revisions are fully corroborated by chemical synthesis.

Acknowledgment. The authors are grateful to UC Berkeley, the ACS-PRF (No. 43546-G1), GlaxoSmithKline, and Boehringer-Ingelheim for support of this research.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0712428

(15) Schill, G.; Logemann, E.; Dietrich, B.; Löwer, H.; Fritz, H. *Synthesis* **1979**, 695−697.

(16) Resubjecting **21** to NaOMe in MeOH resulted in a 2:1 mixture of **21**:**22**.

(17) It has been shown that specific rotation can be highly dependent on concentration and in some cases even changes sign, see: (a) Krow, G.; Hill, R. K. *Chem. Commun.* **1968**, 430−431. (b) Gawley, R. E. *J. Org. Chem.* **2006**, *71*, 2411−2416.