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An epoxide ring-opening approach for a short and stereoselective synthesis of icetexane diterpenoids

Adriana Carita, Antonio C. B. Burtoloso *

Instituto de Química de São Carlos, Universidade de São Paulo, CEP 13560-970 São Carlos, SP, Brazil

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ABSTRACT

A new approach for the synthesis of the core skeleton of icetexane diterpenoids is presented and deals with an epoxide ring-opening reaction by metallated aromatic compounds. Employing this strategy, a short synthesis of an icetexane analogue of brussonol was achieved in just four steps from 2-allylcyclohexanone.

The icetexane diterpenoids encompass a variety of bioactive and structurally interesting compounds.[1] Possessing in its tricyclic skeleton a cyclohexane ring, a central seven-membered ring, and an aromatic ring (or a quinone), these compounds include diterpenes such as brussonol **1**, demethylsalvicanol **2**, salviasperanol **3**, isopisiferin **4**, rosmaridiphenol **5**, barbatusol **6**, cyclocoulterone **7,** and komaroviquinone **8**, among others (Fig. 1).

According to the diverse array of structures found in the icetexanes, it is expected that each subclass of these diterpenes possess different and vast biological activities. In fact, anti-Chagasic, anticancer, antibacterial, antifungal, and anti-Leishmania activities are some of the characteristics found in many of these diterpenes.[1] Considering that, as well as the modest number of different short approaches to prepare such a nice and vast class of compounds described in the literature[2], we decided to investigate the synthesis of the core structure of these diterpenes. We envisioned accomplishing this by employing an epoxide ring-opening reaction as a key strategy[3], followed by Friedel–Crafts or Friedel–Crafts-type cyclization reactions (Scheme 1).

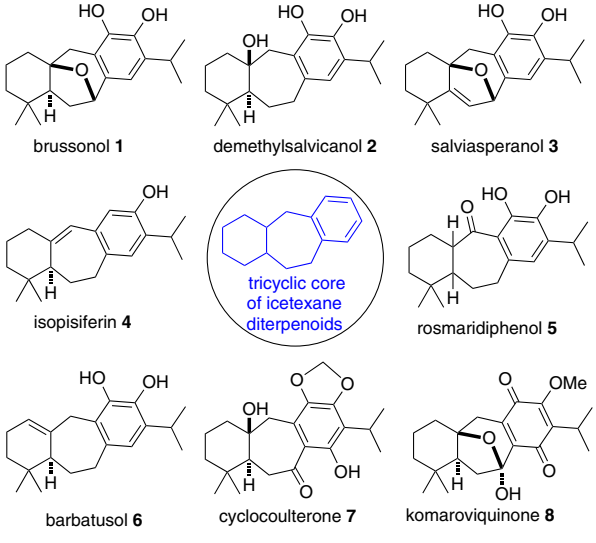
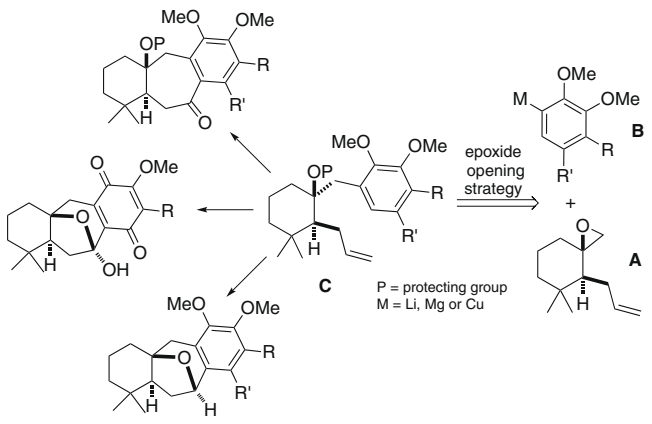


Figure 1. Some icetexane diterpenoids.

It is worth mentioning that intermediates like C were already employed in the total synthesis of important icetexane diterpenes[2a,l], but are generally prepared by multi-step protocols and in low overall yields starting from B. An epoxide strategy, however, would reach the same intermediates in just two steps from a substituted cyclohexanone and would bring all the correct stereocenters attached in the epoxide structure. Herein, we not only



Scheme 1. Epoxide ring-opening approach for the icetexane synthesis.

* Corresponding author. Tel.: +55 16 3373 8641; fax: +55 16 3373 9952.
E-mail address: antonio@iqsc.usp.br (A.C.B. Burtoloso).

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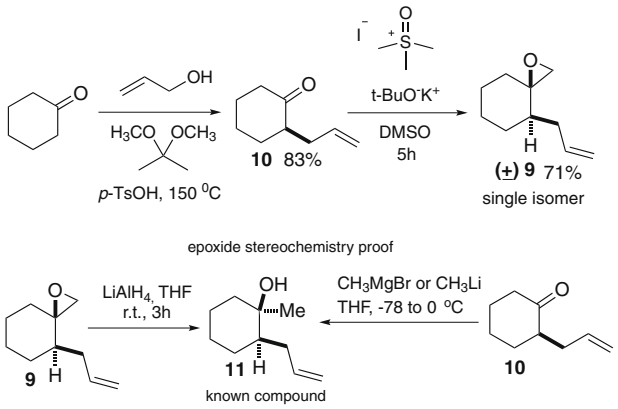


Scheme 2. Synthesis and stereochemistry assign of epoxide **9**.

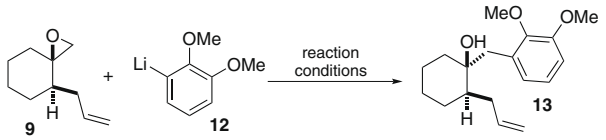
present our results in this epoxide opening strategy, but also show the applicability of this approach by preparing a brussonol analogue in just four steps from commercially available 2-allyl-cyclohexanone.[4]

We started our study by investigating the best reaction conditions for the epoxide ring-opening reaction between racemic epoxide **9** and the lithium anion of 1,2-dimethoxybenzene. Epoxide **9** was readily prepared as a single isomer in just one step from commercially available and easily prepared 2-allyl-cyclohexanone **10**[4], using a Corey–Chaykovsky epoxidation reaction[5] (Scheme 2). Treatment of **10** with trimethylsulfoxonium iodide and potassium *tert*-butoxide, in DMSO, furnished *cis* epoxide **9** in 71%. Although the *cis* stereochemistry outcome is the one expected according to the literature for reactions with mono 2-substituted cyclohexanones and trimethylsulfoxonium iodide[6,7], we decided to prove it by comparative analysis. Since epoxide **9** is unknown, it was converted to its tertiary alcohol derivative, whose ^{1}H and ^{13}C NMR data matched perfectly with the one of known alcohol **11**[8] (Scheme 2).

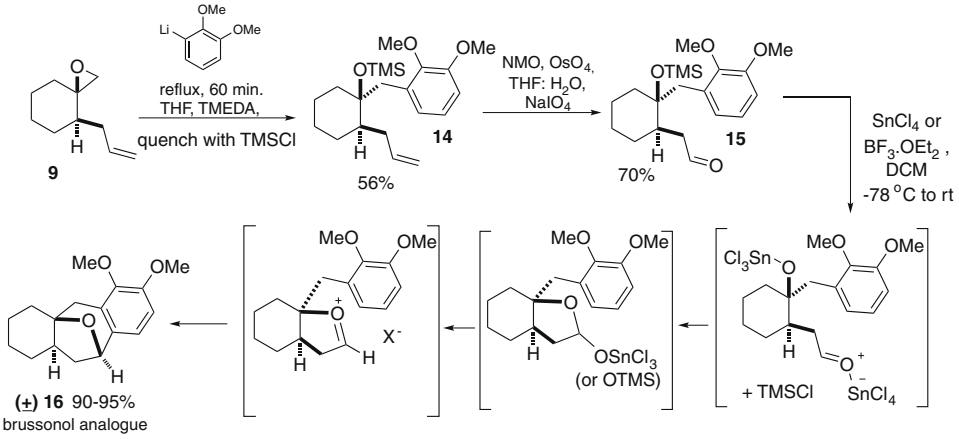
After the synthesis of epoxide **9** and a great number of different employed conditions (Table 1), we found that refluxing **9** and **12** in tetrahydrofuran, in the presence of TMEDA for 1 h, was the best protocol to prepare adduct **13**.[9] Interestingly, when the reaction was carried out at room temperature, an inseparable mixture of **13** and a structurally similar side product was observed. This side product was totally suppressed under heating conditions. In this case, adduct **9** was isolated in 45–55% yield (Table 1, entry 11).

To show the applicability of the present strategy, we decided to convert adduct **13** into aldehyde **15** in order to investigate cyclization approaches toward the icetexane core (Scheme 3). Recently and during the investigation of our work, a total synthesis of brussonol employing an interesting Marson-type Friedel–Crafts alkylation from a methoxy-ketal and $BF_3{\cdot}Et_2O$ was described in the literature.[2l] Based on this work, we wondered if we could employ

Table 1
Epoxide ring-opening study



Entry	Epoxide (equiv)	Lithium anion (equiv)	Reaction conditions	**13** (%)
1	1	1	THF, 25 °C, 8 h	Traces
2	1	2	THF, 25 °C, 8 h	~10%
3	1	2	THF, CuCN, 0–25 °C, 8 h	Traces
4	1	2	THF, TMEDA, CuCN, 0–25 °C, 8 h	Traces
5	1	2	THF, TMEDA, 25 °C, 8 h	20–30%
6	1	2	THF, DMPU, 25 °C, 8 h	Traces
7	1	2	THF, TMEDA, 25 °C, 16 h	~35%
8	2	1	THF, TMEDA, 25 °C, 8 h	~20%
9	1	2	Et_2O, TMEDA, 25 °C, 8 h	~25%
10	1	2	THF, TMEDA, $BF_3{\cdot}Et_2O$, −78–0 °C, 4 h	Traces
11	**1**	**3**	**THF, TMEDA, reflux, 1 h**	**45–55%**
12	1	2	THF, TMEDA, $MgBr_2$, 0–25 °C, 8 h	Traces



Scheme 3. Application of the epoxide ring-opening strategy. Synthesis of a brussonol analogue from epoxide **9**.

the same Marson-type cyclization conditions directly on aldehyde **15** and achieve the synthesis of a brussonol analogue in a tandem fashion. To verify that, TMS-protected aldehyde **15** was prepared in two steps from epoxide **9**, using our epoxide-opening approach, and submitted to the presence of $SnCl_4$ or $BF_3{\cdot}Et_2O$. To our delight, in the presence of these Lewis acids, TMS-protected aldehyde **15** was directly converted in 90–95% yield into brussonol analogue **16** in a possible series of cascade events: (i) removal of TMS; (ii) cyclization to its ketal; (iii) formation of the oxonium ion; and (iv) Marson-type Friedel–Crafts cyclization to **16** (Scheme 3).

As a conclusion, after a thorough investigation, the epoxide ring-opening strategy (key step of the present strategy) was accomplished, furnishing **13** in 45–55% yields. With the present strategy, cyclized product **16** was easily prepared in a short sequence of reactions, employing the conditions (Marson-type cyclization) described by Solorio and Jennings. The use of other epoxides and metallated aromatic rings, and the application of this epoxide ring-opening strategy in the synthesis of other icetexane diterpenes are now being investigated and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (NMR (^{1}H NMR and ^{13}C NMR) and MS spectra for compounds **9**, **11**, **13**, **15** and **16**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.108.

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9. *Experimental procedure for the synthesis of adduct* **13**: To a solution of 1,2-dimethoxybenzene (1.1 mL, 9.0 mmol) in 30 mL of dry tetrahydrofuran (THF), at 0 °C, was added 6.7 mL (9.0 mmol) of a 1.35 M solution of BuLi in hexanes. After stirring the solution for 2.5 h at room temperature, 1.4 mL (9.0 mmol) of tetramethylethylenediamine (TMEDA) was added at once and the solution heated to reflux. Next, 456.0 mg (3.0 mmol) of epoxide **9** in 3.0 mL of dry THF was added and the solution stirred for 1 h under these conditions. The reaction was then cooled to room temperature and 30 mL of saturated NH_4Cl aqueous solution was added to quench the reaction, followed by extraction with EtOAc (3×20 mL). Next, the organic phase was dried with Na_2SO_4, filtered, and evaporated to furnish a crude yellow oil. Column chromatography purification (1:4/EtOAc–hexanes) provided a mixture of tertiary alcohol **13** and remaining 1,2-dimethoxybenzene. Removal of 1,2-dimethoxybenzene (50 °C at 0.1 mmHg or doing a second purification in 3:2/CH_2Cl_2–hexanes, furnished 478.0 mg (55%) of pure alcohol **13**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00–1.80 (3 m, 9H), 2.05 (m, 1H), 2.54 (d, J = 13.5 Hz, 1H), 2.60 (m, 1H), 2.91 (s, 1H, OH), 3.27 (d, J = 13.5 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.90–5.20 (m, 2H), 5.70–6.00 (m, 1H), 6.65–7.05 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8, 25.3, 27.4, 34.1, 36.8, 41.6, 45.5, 55.7, 60.3, 73.5, 110.8, 115.4, 123.8, 124.4, 131.8, 138.7, 147.1, 152.7; IR (neat, cm^{-1}): 3494, 2930, 2854, 1637, 1583, 1477, 1269, 1083, 750, 609; MS-ESI: 313.4 (M+Na), 273.4, 231.4; MS-APCI: 273.1 (M+1−H_2O), 231.1.