Acknowledgements

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Total synthesis of racemic 2-desoxystemodinone and stemodinol; the identity of natural "stemodinol" with stemarin

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Total syntheses of the naturally occurring diterpenoid 2-desoxystemodinone (**3**) and the diterpenoid structure **2** ("stemodinol") are described. The synthetic diterpenoid **2** was not identical to an authentic sample of "stemodinol". The authentic sample was found to be stemarin to which structure **2** had been erroneously assigned in the literature. It would appear that the diterpenoid represented by **2** has not been isolated from natural sources.

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On décrit la synthèse totale du diterpènoïde naturel désoxy-2 stémodinone (**3**) et celle du diterpènoïde ayant la structure **2** ("stémodinol"). Le diterpène synthétique **2** ne correspond pas tout à fait à un échantillon authentique du "stémodinol". On a trouvé que l'échantillon authentique est de la stémarine à laquelle on a attribué par erreur la structure **2** dans la littérature. Il semble donc que le diterpène représenté par la structure **2** n'est pas d'origine naturelle.

[Traduit par le journal]

Recently we described (1) a total synthesis of the structurally unique diterpenoid stemarin (**1**) (2). This synthesis featured photoaddition of allene to an α,β-unsaturated ketone and two subsequent skeletal rearrangements. At the same time (1) we anticipated the completion of syntheses of stemodinol (**2**) (3) and related terpenoids (3, 4) and alphidicolin (5) by a similar strategy.[1] We now wish to describe syntheses of (±)-stemodinol (**2**) and the related diterpenoid (±)-2-desoxystemodinone (**3**) (2) as anticipated.

[1]For syntheses of aphidicolin and the stemodane diterpenoids by entirely different approaches see refs. 6 and 7 respectively.

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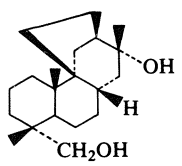

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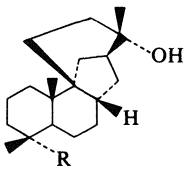
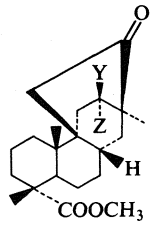
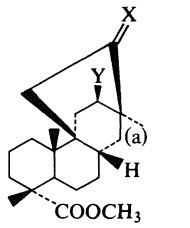


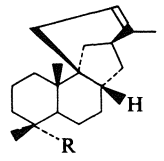
2 R = CH_2OH
3 R = CH_3
12 R = CH_2OTs



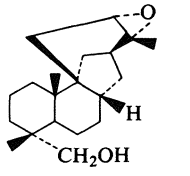
4 Y = H, Z = OH
5 Y = OH, Z = H



6 X = $S(CH_2)S$, Y = OH
7 X = H, H, Y = OH
8 X = H, H, Y = OTs



9 R = $COOCH_3$
10 R = CH_2OH



11

During our synthesis of stemarin (**1**) (1) we encountered a pair of epimeric keto alcohols, **4** and **5**. The former was chosen for conversion into stemarin on the basis of stereochemical considerations and it was predicted (1), on the same basis, that **5** could readily be converted into stemodinol (**2**). The validity of this prediction has now been demonstrated by the successful conversion of **5** into **2** and **3** as described in the sequel.[2]

The keto alcohol **5** (mp 191°C; spectral properties similar to **4** (1)) was converted, quantitatively, into the thioketal **6** (mp 177–178°C; nmr δ: 3.17 (m, 4H, ethylene of ketal)) which, on treatment with Raney nickel, afforded (97%) the alcohol **7** (mp 130°C; ir: 3500 (OH) and 1705 (ester) cm^{-1}; nmr δ: 3.56 (m, 1H, H—C—OH)). The latter was converted into the gummy tosylate **8** (nmr δ: aromatic protons 7.20–7.85) in which the tosylate group was *anti* and periplanar to the bond (a), the required stereoalignment for the desired rearrangement (*vide infra*).

When **8** was heated at 60°C in DMSO in the presence of methyl sulfinyl carbanion (8), it was transformed, by migration of bond (a) and elimination of hydrogen, into the olefin **9** (oil; ir (film): 1730 (ester) and 1650 (olefin) cm^{-1}; nmr δ: 1.55 (d, $J = 2$ Hz, 3H, vinylic methyl and 4.94 (m, H, vinylic proton)), which was reduced quantitatively with $LiAlH_4$ to the olefinic alcohol **10** (oil; ir (film): 3350 (OH) and 1625 (olefin) cm^{-1}; nmr δ: 3.07 and 3.38 (doublets, $J = 11$ Hz, 1H each, CH_2—OH)).

Epoxidation of **10** with *m*-chlorobenzoic acid gave the oily epoxide **11** (68%; nmr δ: 1.27 (s, 3H, methyl attached to oxirane ring)). The oxirane ring was assigned the α-configuration on the basis of conversion of **11** into 2-desoxystemodinone (**3**) (2) (*vide infra*). Finally, reduction of **11** with $LiAlH_4$ afforded the racemic diterpenoid **2** (mp 160°C; ir: 3510 and 3350 (OH) cm^{-1}; nmr δ: 0.82, 1.00 and 1.11 (singlets, 3H each, tertiary methyls), 3.07 and 3.37 (doublets, $J = 11$Hz, 1H each, CH_2—OH)).

The synthetic diterpenoid (**2**) was clearly *not identical* with a sample of "stemodinol" from natural sources. Eventually, by comparison with authentic stemarin (**1**), it was discovered that the sample of naturally occurrring stemodinol (3) which we received was in fact stemarin (**1**).[3] To the best of our knowledge the diterpenoid having structure **2** ("stemodinol") has not been isolated from natural sources.

We were now faced with the necessity of demonstrating the validity of structure **2** for our synthetic diterpenoid, a task which was complicated by our inability to produce crystals of **2** or its derivatives suitable for X-ray crystallographic analysis. Eventually this task was accomplished in the following manner. The tosylate **12** of **2** was reduced with $LiAlH_4$ and the product (**3**) was shown to be identical (ir, nmr, ms, and silica gel tlc) with an authentic sample of the naturally occurring 2-desoxystemodinone (2), the structure of which has been unequivocally shown to be **3**.[4] The assignment of the CH_2OH group in **2** to the α-orientation follows from the fact that **2** and stemarin have been synthesized from common intermediates (1). Thus, the conversion of **2** to **3** proves that structure **2** is correct for our synthetic diterpenoid and constitutes a total synthesis of 2-desoxystemodinone (**3**).

Acknowledgments

We thank the Natural Sciences and Engineering

[2]Throughout, the ir spectra (in Nujol unless specified) and the nmr spectra (in $CDCl_3$) are entirely consistent with assigned structures. Satisfactory elemental analyses were obtained for all crystalline compounds and correct molecular ions were found in the mass spectra of the remaining compounds.

[3]Professor C. D. Hufford, University of Mississippi, University, Mississippi, concurs with the results of our comparison.

[4]Details to be published elsewhere.

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