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Organozirconium Methods for the Efficient Construction of the Bicyclo[9.3.0]tetradecane Dolabellane Skeleton

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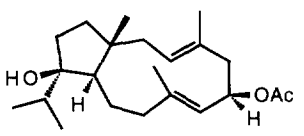
Abstract: Two highly convergent routes to the acetoxyodontoschismenol dolabellane skeleton are described. Both utilise efficient organozirconium based coupling reactions to rapidly assemble macrocyclisation precursors. The first approach closes the key eleven membered ring of the dolabellane skeleton by an intramolecular Nozaki - Hiyama reaction, whereas the second uses an intramolecular α-sulphonyl carbanion - allyl iodide condensation. Copyright © 1996 Elsevier Science Ltd

Introduction

The first reported isolation of a natural product from the dolabellane class of diterpenoids appeared in 1976.[1] In the succeeding period, a wide variety of dolabellane structures have been determined, including acetoxyodontoschismenol **1**,[2] stolonidiol **2**[3] and dolabella-2,7-dien-9-one **3**.[4] Most dolabellanes exhibit antimicrobial activity, and many have been shown to possess potency against tumours or the influenza virus. Dolabellanes are also the biogenetic and chemical precursors of several other diterpene classes including the dolastanes[5] through transannular cyclisations. The first total syntheses of dolabellane natural products were recently disclosed.[6] Although diverse in the range of additional functionality present, all dolabellanes are based around the bicyclo[9.3.0]tetradecane skeleton. We recently reported[7] the development of a tandem insertion (allyl carbenoid + electrophile) protocol for the efficient elaboration of zirconacycles. Herein we describe application of this methodology to the synthesis of the dolabellane skeleton, in particular to close analogues of acetoxyodontoschismenol **1**. Our methodology allowed the rapid assembly of two cyclopentanoid based macrocyclisation precursors. Two different cyclisation strategies were employed which formed the basis of routes 1 and 2, described below.



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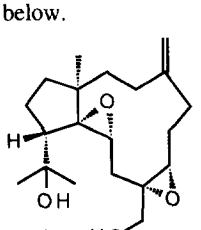

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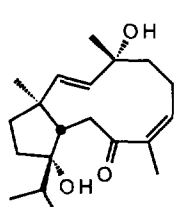

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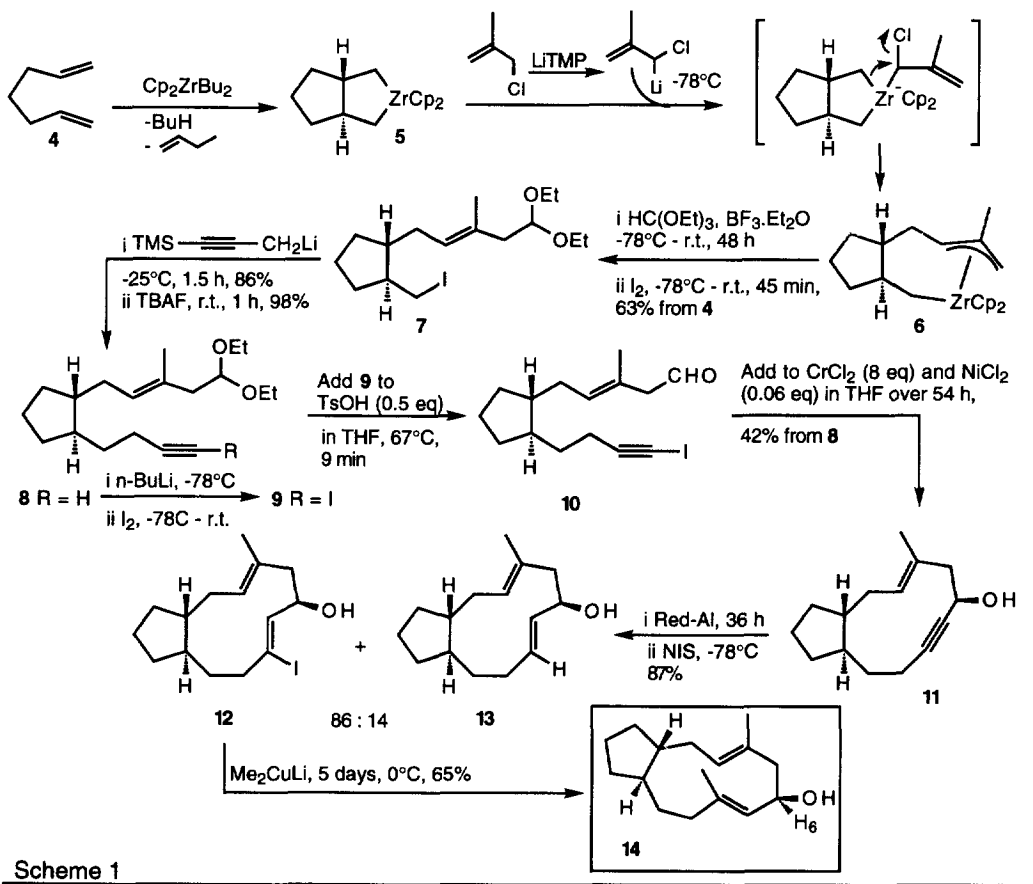
Construction of the Bicyclo[9.3.0]tetradecane Dolabellane Skeleton - Route 1.

Zirconocene (1-butene) mediated co-cyclisation of 1,6-heptadiene[8] **4** afforded the known zirconacyclopentane **5** (**Scheme 1**). Insertion of lithium chloromethallylide[7b] gave methallyl zirconocene complex **6** in quantitative yield. Further reaction with triethylorthoformate[7c] afforded, after iodinolytic work-up, iodide **7** in good overall yield for this single pot process (**4** - **7**, 63%). Homologation with lithiated

1-(trimethylsilyl)-1-propyne[9] and subsequent desilylation using TBAF gave alkyne **8**[10] in excellent yield. Conversion to alkynyl iodide **9** was effected quantitatively by deprotonation / iodine quench. Deprotection of the β, γ-unsaturated acetal moiety in **9** without migration of the olefin into conjugation with the resulting aldehyde proved challenging. Eventually, the selective acetal deprotection was achieved *via* reaction with *p*-toluenesulphonic acid (0.5 eq) in THF at reflux under carefully controlled conditions. With the sensitive 1-iodo-11-al **10** in hand we were in a position to attempt macrocyclisation reactions.

We hoped to close the desired eleven membered ring *via* an intramolecular Nozaki - Hiyama reaction,[11] mediated by Cr(II). Indeed, we were delighted to find slow addition (54 h) of a dilute solution of **10** (0.1 M) to a dilute suspension of $CrCl_2$ (8 eq) / $NiCl_2$ (0.06 eq) in THF, under a modification of the conditions reported by Keese[11d], afforded macrocycle **11** in good yield, pleasingly as a single diastereomer. The strong conformational preferences of the 11 member rings in the dolabellanes are well known,[2b,c] and would be expected to be reflected in a well defined transition state for the macrocycle ring closure.

Conversion of alkyne **11** to the trisubstituted alkene found in **1** was achieved using a hydroalumination - iodination procedure.[12] Reaction of **11** with Red-Al®,[12c] followed by iodine[12d] or N-iodosuccinimide (NIS)[12e] afforded variable mixtures of iodide **12** and the unwanted protonation product **13**. Better results were obtained with NIS (**12** : **13** = 84 : 16, 87% yield). Displacement of the vinyl iodide with lithium dimethylcuprate[13] gave the target molecule, acetoxyodontoschismenol analogue **14**, in good yield after chromatography, contaminated only with trace amounts (ca 5%) of **13**. We were pleased to assign the stereochemistry of the secondary alcohol in **14** to be as that found in **1** by comparison of spectral data[14] with



Scheme 1

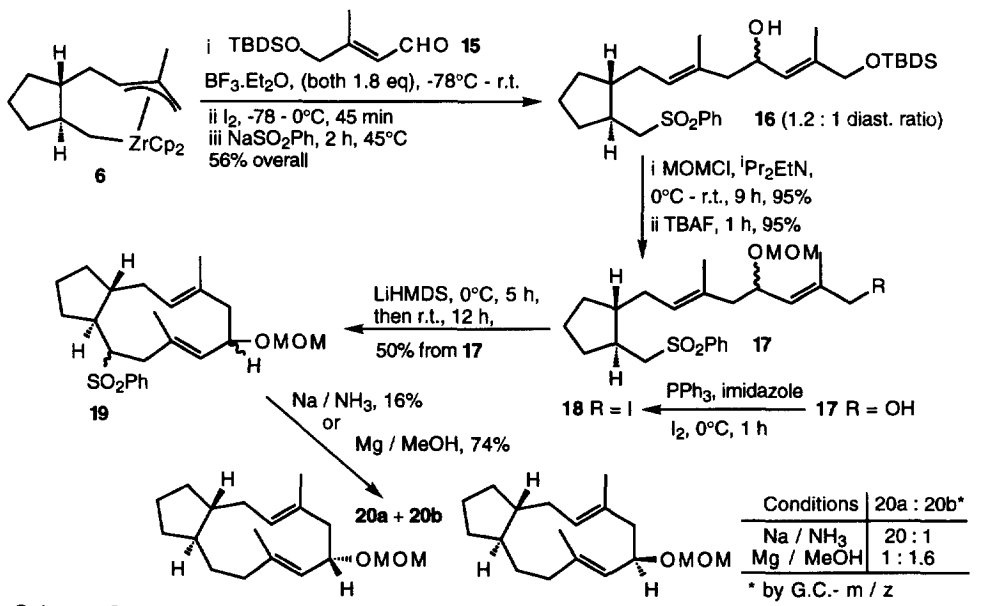
that reported for the acetate hydrolysis product of **1**.[2b]

Route 1 therefore represents a highly efficient and stereoselective eight pot (11% overall yield) synthesis of the dolabellane analogue **14**, containing the key bicyclo[9.3.0]tetradecane skeleton.

Construction of the Bicyclo[9.3.0]tetradecane Dolabellane Skeleton - Route 2.

We were delighted with the construction of the dolabellane skeleton (route 1), however we were keen to formulate an alternative and more convergent route avoiding the use of triethylorthoformate and Me_2CuLi as inefficient C_1 synthons. Indeed, Lewis acid catalysed reaction of methallyl zirconocene complex **6** with aldehyde **15**[15] afforded, after iodinolytic work-up and sulphone formation, **16** in excellent overall yield as a 1.2 : 1 mixture of diastereomers. The zirconocene template had mediated the assembly of all the carbons required for the dolabellane skeleton in a single pot. A simple protection - deprotection sequence followed by conversion of the allylic alcohol **17** to allylic iodide **18** using the mild procedure of Corey[16] gave our cyclisation precursor. It was hoped that generation of an α-sulphonyl carbanion would effect displacement of the allylic iodide,[17] forming the desired eleven membered ring. Indeed, slow addition (5.5 h) of lithium hexamethyldisilazide (LiHMDS, 0.1 M) to a dilute solution of **18** (5 x 10^{-6} M) in THF[17d] afforded **19** in good yield, as a mixture of diastereomers. Desulphonylation was initially attempted under conditions described by Marshall[17b] (Na / NH_3). Unfortunately, the reaction was low yielding, almost exclusively destroying one product diastereomer (**20b**) by cleavage of the allylic C-O bond. Desulphonylation using the method of Carpino[18] (Mg / MeOH) gave higher yields, affording **20** as a mixture of two diastereomers (**a** : **b** = 1 : 1.6). The major diastereomer (**20b**) was shown have the desired secondary alcohol stereochemistry by correlation of spectral data with that obtained for the MOM ether derivative of **14** prepared in route 1.

Although not stereoselective, route 2 represents an extremely convergent five pot (19% overall yield) synthesis of the key bicyclo[9.3.0]tetradecane dolabellane skeleton.



Scheme 2

Conclusion

The tandem elaboration protocol for zirconacyclopentanes has been applied to two efficient syntheses of the dolabellane bicyclo[9.3.0]tetradecane skeleton. The first route utilised an intramolecular Nozaki - Hiyama reaction for the key 11 membered ring closure, and was totally stereoselective. The second route used an

α-lithiosulphone - allyl iodide ring closure and, although not totally stereoselective, assembled all the carbons required from 3 components in a single pot.

Acknowledgements

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