Sequential ring closure and [2,3]-sigmatropic rearrangement reactions: an approach to the synthesis of C-19 oxygenated cyathane-type diterpenoids

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Preparation of the tertiary allylic alcohols 17–22, followed by subjection of these substances to the Still–Mitra [2,3]-sigmatropic rearrangement sequence, provides the functionalised bicyclo[4.3.0]nonanes 23–26; acquisition of 26 points to a strategy for the synthesis of C-19 oxygenated cyathane-type diterpenoids.

Members of the cyathane family of diterpenoids share the tricyclic carbon skeleton shown in **1**.† Although many of the cyathanes are highly oxygenated, particularly on ring C, very few have oxygen functions associated with the C-3 isopropyl group. Examples of C-19 hydroxylated compounds belonging to this class include cyathin A_4 (**2**),[3] sarcodonin G (**3**)[1b] and sarcodonin A (**4**).[1b] Although the configuration at C-18 of **2** was not determined,[3] an X-ray crystallographic analysis of a derivative of sarcodonin G established that this natural product and, presumably, the related substance sarcodonin A, possess the absolute configurations shown in formulas **3** and **4**, respectively.[1b]

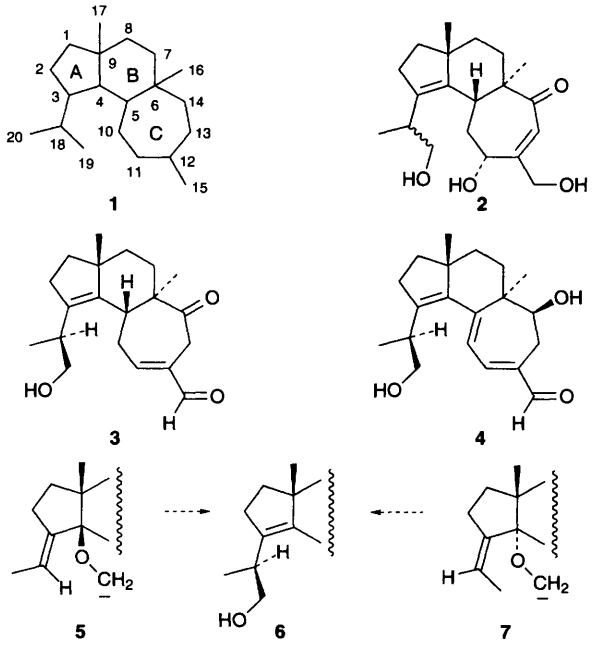
From a synthetic viewpoint, the presence of the C-18 stereogenic centre in substances such as **2–4** translates into a complexity not present in cyathanes that possess at C-3 an unoxygenated isopropyl group. On the other hand, the fact that **2–4** also contain a C-3–C-4 double bond suggests that a synthetic approach to the ring A functionality of these materials could involve a [2,3]-sigmatropic rearrangement strategy. For example, successful bond reorganisation of each of the isomeric anions of general structure **5** and **7** would provide a product **6** having the correct relative configurations at C-9 and C-18 (cyathane numbering). We report herein the results of a study that shows the viability of this strategy.‡

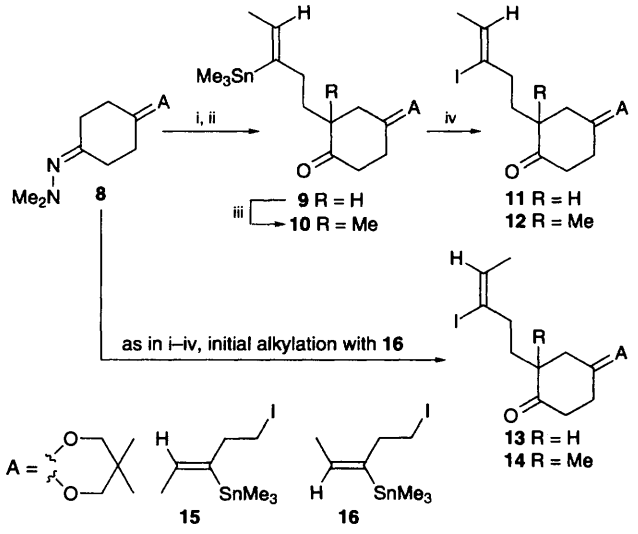
The keto alkenyl iodides **11–14** employed in this study were prepared as shown in Scheme 1.§ Alkylation[5] of the hydrazone **8** with the iodide **15**,¶ followed by cleavage of the hydrazone function,[5] provided (78%) the keto trimethylstannane **9**. Methylation of **9** afforded **10** (66%). Iodostannylation of **9** and **10** to give **11** and **12** was readily achieved in yields exceeding 90%. In a similar fashion, employing the iodide **16**¶ as the initial alkylating agent, the substrates **13** and **14** were also prepared from the hydrazone **8** (Scheme 1). The reaction yields were similar to those involved in the conversion of **8** into **11** and **12**.

Treatment of the keto iodide **11** with BuLi (4 equiv.‖) afforded in 84% yield a mixture of two products, **17** and **18**, in a ratio of about 20 : 1 (Scheme 2). Flash chromatography[7] of this mixture on silica gel allowed the isolation of pure **17** and **18**. BuLi-mediated ring closure of the substrate **13** (geometric isomer of **11**) produced a mixture of the alcohols **19** and **20** (ratio ~4 : 1) in 78% yield. Separation of these substances was achieved by flash chromatography.[7]

In contrast to the substrates **11** and **13**, which produced mixtures of diastereoisomers containing a preponderance of the *trans*-fused products **17** and **19**, respectively, BuLi-mediated cyclisation of substances **12** and **14** gave, in each case, a single bicyclic product. Based on an examination of molecular models, it was not surprising to find (*vide infra*) that both of the products **21** and **22** are *cis*-fused (Scheme 2). The isolated yields of these materials were 58 and 72%, respectively.

Sequential treatment[8] of the tertiary allylic alcohol **17** with KH and iodomethyl(tributyl)stannane, followed by addition of BuLi, provided, in 63% yield, the bicyclic alcohol **23**** (Scheme 2). As expected,[8] the same product **23** (56% yield) was





Scheme 1 *Reagents and conditions*: i, BuLi, THF, 0 °C; DMPU, **15**, 35 °C; ii, $NaIO_4$, THF, H_2O, KH_2PO_4–NaOH–H_2O buffer (pH 7.2), 40 °C; iii, KOBu^t, THF, HMPA, 60 °C; MeI; iv, I_2, CH_2Cl_2, room temp.

derived from subjection of the substrate **20** to a similar reaction protocol. On the other hand, the allylic alcohols **18** and **19** (epimers of **17** and **20**, respectively) were transformed into **24**, which is epimeric with **23**.

With respect to an approach to the synthesis of C-19 oxygenated cyathane-type diterpenoids, the stereospecific transformations of **21** and **22** into the corresponding alcohols **25** and **26** are particularly important. Conversion of the starting materials into the corresponding (tributylstannyl)methyl ethers, followed by the [2,3]-sigmatropic rearrangement reactions, afforded the products **25** and **26** in yields of 52 and 46%, respectively. It should be noted that the Still–Mitra rearrangement[8] has been previously achieved on tertiary allylic *acyclic* alcohols.[9] On the other hand, the rearrangement sequences outlined above involve substrates (**17–22**) in which the allylic hydroxy groups are, in each case, at an angular position of a bicyclic carbon framework. Indeed, the conversions of **21** and **22** into **25** and **26**, respectively, are especially noteworthy since, in these cases, the hydroxy groups of the starting materials are, in addition, adjacent to quaternary carbon centres.

The relative configurations of substances **17–26** were determined by performing two key X-ray crystallographic studies.†† One of these, carried out on the tertiary allylic alcohol **21** (mp 88–89 °C) obtained from cyclisation of **12**, showed that the former compound possesses a *cis*-fused ring junction. Since the Still–Mitra rearrangement of **22** provided a product diastereoisomeric with that derived from **21**, the alcohol **22** must also be *cis*-fused.‡‡

The alcohol (mp 84–85 °C) derived from subjecting either **17** or **20** to the [2,3]-sigmatropic rearrangement sequence was shown by X-ray analysis to possess the relative configuration shown in formula **23**. Therefore, the major product **17** obtained from BuLi-mediated ring closure of **11** must be *trans*-fused, while the minor product derived from **13** must possess the *cis*-fused structure shown in formula **20**. These experiments, in turn, established the relative configuration of each of the substances **18**, **19** and **24**.

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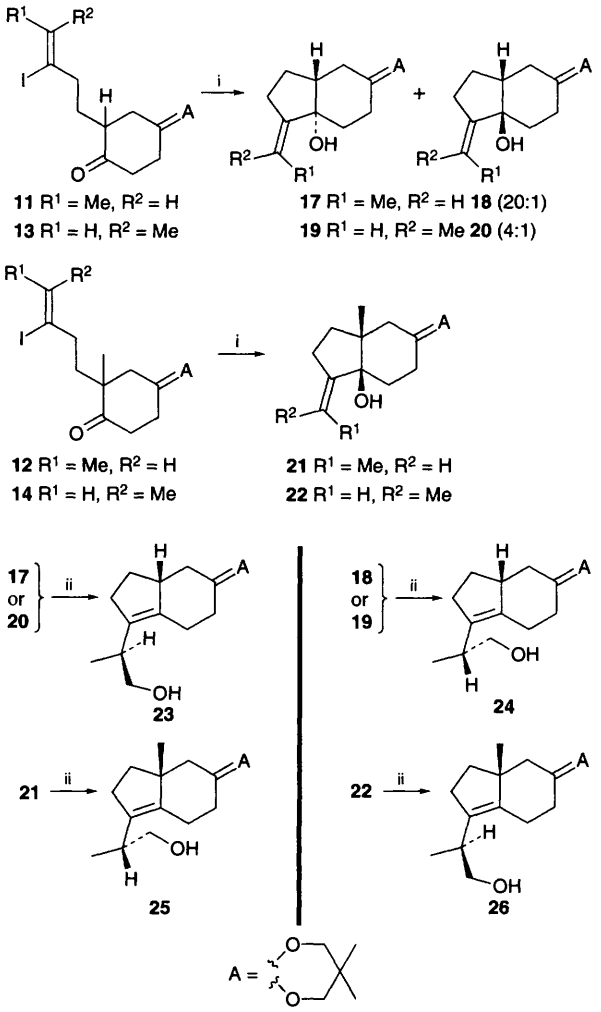

Scheme 2 *Reagents and conditions*: i, BuLi (4 equiv.), THF, −78 °C, then H_2O; ii, KH (1.1–1.5 equiv.), THF, room temp.; 18-crown-6 (2 equiv., for substrates **18** and **20–22** only); Bu_3SnCH_2I (2–4 equiv.), room temp.; BuLi (4–6 equiv.), −78 °C to room temp., then H_2O

Footnotes

† For key reports on the isolation and structural elucidation of cyathane-type terpenoids, see ref. 1. The numbering system shown in **1** is that originally suggested by Ayer (ref. 2)

‡ For previous reports related to the synthesis of cyathane-type terpenoids, see ref. 4.

§ All new compounds reported herein exhibit spectra in accord with the assigned structures and gave satisfactory elemental (C, H) analyses and/or molecular mass determinations (high resolution mass spectrometry).

¶ The homoallylic iodides **15** and **16** were prepared by reaction (room temperature) of the corresponding alcohols (ref. 6) with $Ph_3P{\cdot}I_2$ in CH_2Cl_2 in the presence of Et_3N.

‖ Use of fewer than 4 equiv. of BuLi gave incomplete lithium–iodine exchange. Presumably, a portion of the alkyllithium was unavailable for the exchange reaction due to complexation with the ketal function present in the substrate.

** Also obtained from this reaction sequence was a significant amount (33%) of the methyl ether of the starting material. A similar pattern was observed for the other rearrangement processes. The isolated yields of the bicyclic alcohols **24–26** were in the range 46–53%.

†† We thank Dr Steven J. Rettig for carrying out these X-ray crystallographic structure determinations. Details of these studies will be reported elsewhere.

‡‡ This conclusion, along with those given in the following paragraph, is based on the well-established stereochemically related characteristics of the [2,3]-sigmatropic rearrangement process [ref. 8(*b*)].

References

1 (*a*) W. A. Ayer and S. P. Lee, *Can. J. Chem.*, 1979, **57**, 3332; (*b*) H. Shibata, T. Tokunaga, D. Karasawa, A. Hirota, M. Nakayama, H. Nozaki and T. Tada, *Agric. Biol. Chem.*, 1989, **53**, 3373; (*c*) H. Kawagishi, A. Shimada, R. Shirai, K. Okamoto, F. Ojima, H. Sakamoto, Y. Ishiguro and S. Furukawa, *Tetrahedron Lett.*, 1994, **35**, 1569; (*d*) R. S. Compagnone and D. J. Faulkner, *J. Nat. Prod.*, 1995, **58**, 145.

2 W. A. Ayer and H. Taube, *Tetrahedron Lett.*, 1972, 1917.

3 W. A. Ayer, L. M. Browne, J. R. Mercer, D. R. Taylor and D. E. Ward, *Can. J. Chem.*, 1978, **56**, 717.

4 W. A. Ayer, D. E. Ward, L. M. Browne, L. T. J. Delbaere and Y. Hoyano, *Can. J. Chem.*, 1981, **59**, 2665; D. E. Ward, *Can. J. Chem.*, 1987, **65**, 2380; K. R. Dahnke and L. A. Paquette, *J. Org. Chem.*, 1994, **59**, 885.

5 E. J. Corey and D. Enders, *Chem. Ber.*, 1978, **111**, 1337.

6 E. Piers and A. V. Gavai, *J. Org. Chem.*, 1990, **55**, 2380.

7 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

8 (*a*) W. C. Still and A. Mitra, *J. Am. Chem. Soc.*, 1978, **100**, 1927; (*b*) T. Nakai and K. Mikami, *Org. React.*, 1994, **46**, 105.

9 M. Balestra and J. Kallmerten, *Tetrahedron Lett.*, 1988, **29**, 6901.

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