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Tetrahedron Letters 47 (2006) 1453–1455
Tetrahedron Letters

Enantioselective synthesis of the bicyclo[4.3.0]nonane ring system of the pinguisane-type sesquiterpenoids via a Brønsted acid promoted transannular enol alkylation

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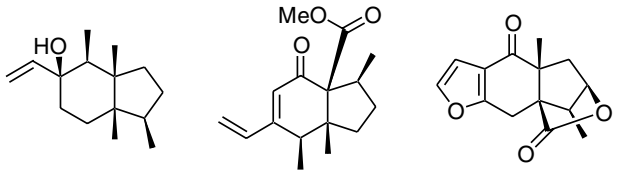
Received 21 November 2005; accepted 14 December 2005

Abstract—The bicyclo[4.3.0]nonane ring system of the pinguisane-type sesquiterpenoid natural products, including the vicinal quaternary stereocentres, has been synthesised as a single enantiomer via a novel Brønsted acid promoted transannular alkylation of an enol with an unactivated alkene.

A wide range of sesquiterpenes possessing the bicyclo[4.3.0]nonane ring system have been isolated from liverworts (Fig. 1),[1] and some of these compounds have been shown to have anticancer,[2] antimicrobial[3] and antifeedant activities.[4] The key structural features of this class of natural product is the dense array of stereogenic centres around the bicyclo[4.3.0]nonane system, particularly the presence of two vicinal quaternary stereogenic carbons at the 6, 5 ring junction. This array of stereogenicity and the presence of the two quaternary centres has made the synthesis of this class of natural product a significant challenge.



pinguisenol acutifolone A norpinguisanolide

Figure 1.

To date there have been far general strategies, which have been used to construct the ring systems present in these natural products, including annulation of a pre-existing cyclohexanone unit,[5] intramolecular Diels–Alder cyclisations,[6] cycloisomerisations[7] and cationic cyclisations.[8] However, these strategies require a large number of chemical steps in order to set up the bicyclo[4.3.0]nonane ring system and to install the vicinal quaternary centres. To our knowledge, only the annulation strategy has provided an enantioselective route to this class of molecule.[5e,f]

We had an interest in the use of transannular cyclisation reactions for the construction of bicyclic ring systems and were interested in developing such a strategy for the synthesis of the bicyclo[4.3.0]nonane unit replete with the vicinal quaternary stereocentres and functionality, which would allow for the conversion of the cyclisation product into one or more of the pinguisane-type sesquiterpenes. Additionally, we wished for this route to provide a single enantiomer of the bicyclo[4.3.0]nonane unit. As we had some experience of transannular cyclisations across nine-membered rings we opted to break retrosynthetically the carbon–carbon bond common to both the five- and six-membered rings, thus revealing a cyclononene ring **2** as a bicyclo[4.3.0]nonane precursor (Fig. 2). We were attracted to a system such as **2** as it was reminiscent of the nine-membered ring **3** we had prepared in our synthesis of the DEF-rings of hexacyclinic acid and FR182877. In order to assess the feasibility of this transannulation strategy for the construction

Keywords: Pinguisane sesquiterpenoids; Transannular cyclisations; Enol alkylation; Brønsted acid; Vicinal quaternary centres.
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doi:10.1016/j.tetlet.2005.12.084

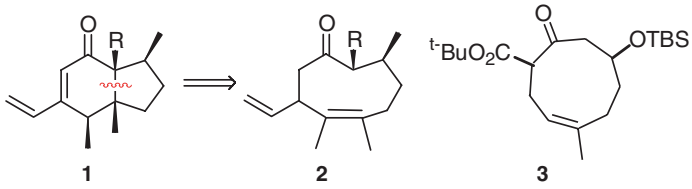
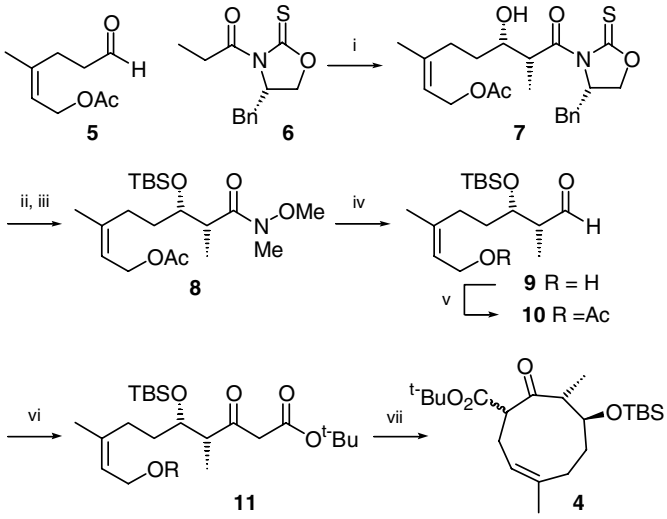


Figure 2.



Scheme 1. Reagents and conditions: (i) $TiCl_4$, (−)-sparteine, CH_2Cl_2, −78 to 0 °C, 78%; (ii) MeNHOMe·HCl, Me_3Al, THF, −20 °C; (iii) TBSCl, imidazole, DMF, 71% (over two steps); (iv) DIBAL-H, THF, −78 °C, 48% (**9**) and 43% (**10**); (v) Ac_2O, Et_3N, CH_2Cl_2, $NaHCO_3$, 0 °C to rt, 90%; (vi) $SnCl_2$, $^tBuO_2CCHN_2$, CH_2Cl_2, 89%; (vii) NaH, $Pd(PPh_3)_4$, dppe, THF, reflux, 47%.

of the bicyclo[4.3.0]nonane unit with the vicinal quaternary stereocentres we envisaged modifying our previous route to construct cyclisation precursor **4** (Scheme 1). While **4** does not contain all the elements necessary to enable the elaboration of the transannular cyclisation product into the natural products, it does provide us with an opportunity to access the feasibility of our strategy using a molecule, which we had to hand as part of our investigations on the hexacyclinic acid[9,10] and FR182877 structures.[10,11]

Our synthesis of **4** (Scheme 1) began by conducting an 'Evans-like' aldol reaction of oxazolidinethione **6** with aldehyde **5** under conditions reported by Crimmins,[12] which produced the all *syn*-aldol product **7** in 78% yield as a single diastereomer. Weinreb amide formation and silyl protection of the alcohol proceeded smoothly and in 71% yield over the two steps. Reduction of the Weinreb amide to the aldehyde was achieved by use of DIBAL-H and furnished essentially a 1:1 mixture of **9** and **10**. The free allylic alcohol in **9** was re-acylated to provide **10** in a 90% yield. The β-ketoester **11** was installed by treatment of **10** with *tert*-butyl diazoacetate and $SnCl_2$. Finally, closure of the nine-membered ring was achieved by use of our previously reported conditions.[10] This furnished **4** in a disappointing, but adequate, 47% yield.

In earlier studies we had shown that similar systems underwent transannular cyclisations of the various oxygen functionalities around the nine-membered ring, to form either ether or lactone containing products.[10] We required that the enolisation occurs between C(1) and C(2) so that transannulation may occur to form the bicyclo[4.3.0]nonane system (Fig. 3), rather than between C(9) and C(1), which would probably not lead to any cyclisation product.

In order to prevent cyclisation via oxygen and enolisation between C(9) and C(1), we opted to form lactone **13** (Scheme 2), which was prepared in 71% yield by HF deprotection of the silyl ether and removal of the

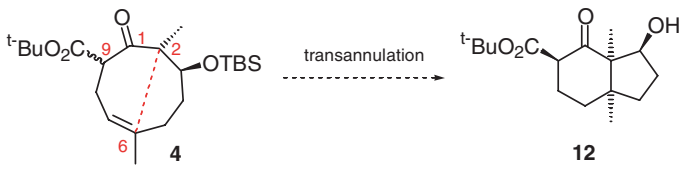
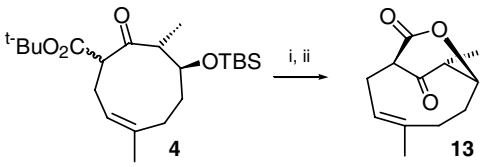


Figure 3.



Scheme 2. Reagents and conditions: (i) HF, MeCN; (ii) TFA, CH_2Cl_2, 71% (over two steps).

tert-butyl ester and in situ lactonisation with TFA. An X-ray crystal structure of **13** revealed that the ketone carbonyl and H(2) were appropriately aligned for enolisation to occur (Fig. 4), if conditions could be found. We were confident that enolisation would not occur between C(9) and C(1) as that would necessitate the formation of an *anti*-Bredt bridgehead double bond.

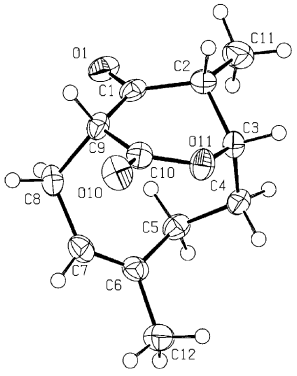
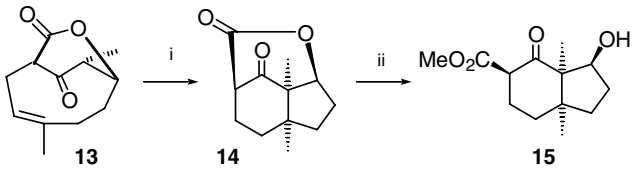


Figure 4. X-ray structure of lactone **13**.

We rationalised that a Brønsted acid capable of promoting enolisation as well as protonation of the double bond on the other side of the ring would stand the best chance of success. To this end we treated **13** with 15 eq. of HBF_4 in Et_2O/AcOH, and we were delighted to witness the clean formation of a new product, which was identified by comprehensive NMR spectroscopy and X-ray crystallography as the desired bicyclo-[4.3.0]nonane ring system **14** (Scheme 3, Fig. 5). The lactone was opened with NaOMe in MeOH to yield the bicyclo[4.3.0]nonane core of the pinguisane-type sesquiterpenoids complete with the vicinal quaternary centres, as a single enantiomer.



Scheme 3. Reagents and conditions: (i) 54% HBF_4 in Et_2O, AcOH, 66%; (ii) NaOMe, MeOH, 70%.

In conclusion, we have developed a conceptually novel asymmetric approach to the construction of the bicyclo[4.3.0]nonane ring systems of the pinguisane-type sesquiterpenoids, by use of a Brønsted acid promoted transannular cyclisation of an enol onto an unactivated

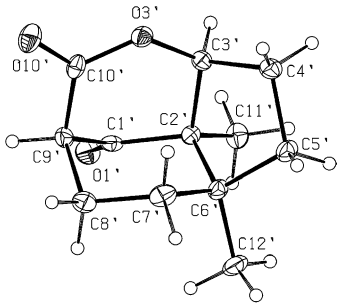


Figure 5. X-ray structure of compound **14**.

carbon–carbon double bond. This extends the scope of transannulation reactions in the synthesis of complex and biologically active natural products. Work is on going to apply this strategy to the synthesis of pinguisenol and acutifolone A, and these studies will be reported in due course.

Acknowledgements

We thank the EPSRC and Pfizer for studentship funding (R.J.G.B.) and AstraZeneca for an unrestricted research award (P.A.C.).

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