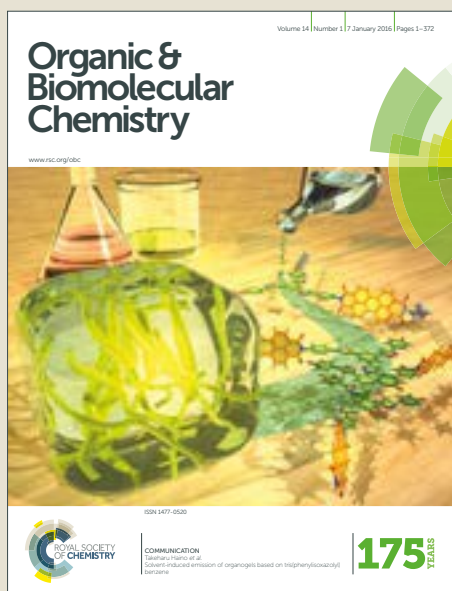


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A New Route to Tricyclane Sesquiterpenoids: Total Synthesis of α -Ekasantalic acid

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Chemical manipulation of the cycloadduct of citraconic anhydride and cyclopentadiene enables a new synthetic route to tricyclane sesquiterpenoids. This methodology is applied to the first total synthesis of α -ekasantalic acid.

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Introduction

Tricyclane sesquiterpenoids (**Figure 1**) are a family of nearly 100 natural products isolated from plant sources. The principle characteristic feature of this natural product family is the presence of a tricyclo[2.2.1.0^{2,6}]heptane (tricyclane) ring within their structure. α -Santalene, **1**,¹⁻³ and its analogues, e.g. **2-4**,⁴⁻⁷ represent the most common skeleton in this family, although other skeletons, as exemplified by cyclosinularane, **5**,⁸ cycloseychellene, **6**,⁹ and cyclomytlayan-5 α -ol, **7**,^{10,11} are also reported. A handful of molecules in this family contain a fourth ring leading to compact and complex skeletons comprising of several quaternary carbon atoms. These include longicyclene, **8**,^{12,13} and its analogues **9**,¹⁴ and **10**;^{12,13} cyclosativene, **11**,¹⁵⁻²¹ cyclocopacamphene, **12**,^{19,22} and dendronobilin N, **13**.²³

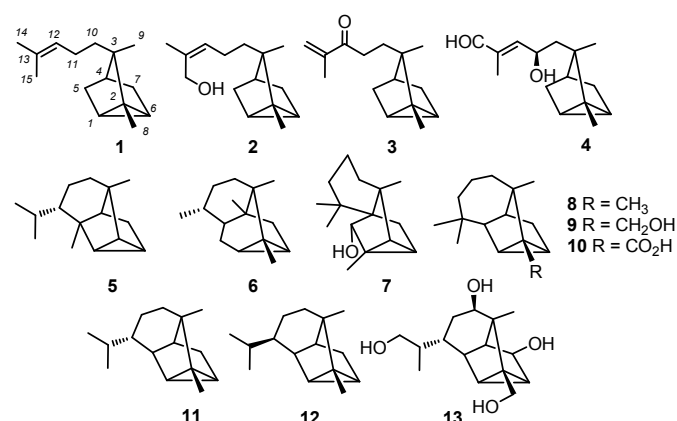


Figure 1 Tricyclane sesquiterpenoid family and related compounds.

Traditionally, tricyclane sesquiterpenoids' main use has been in the perfumery and flavouring industries, although many plant extracts that do contain them have also been used in

traditional medicine.²⁴⁻²⁶ More recently, individual molecules with antifungal, antibacterial and antitumor properties are reported in the literature. For example, α -santalol, **2**, binds to tubulin and cause G2/M cell cycle arrest in a panel of head and neck cancer cell lines⁵ and HL-60 leukaemia cells;⁴ inhibits migration of MCF-7 and MDA-MB-231 breast cancer cells by targeting the β -catenin pathway;²⁷ and is an antagonist of D₂ and 5-HT_{2A} receptors.²⁸ Compound **2** is also shown to be mildly active against *Helicobacter pylori*⁶ whilst compound **3** is reported to have antimicrobial activity against the oral pathogen *Porphyromonas gingivalis*.⁷ Compound **4** is a pro-apoptotic cytotoxin at sub μ M concentrations,²⁹ showing selectivity for tumour cells against healthy ones; and compound **10**, a metabolite of longicyclene, suppresses the SOS response induced by chemical mutagens.³⁰

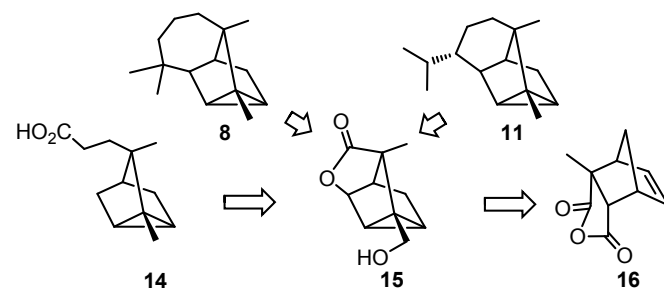


Figure 2 Proposed synthetic route to tricyclane α -ekasantalic acid, **14**, and to tetracyclane sesquiterpenoids.

Further understanding of the mode of action of this rare class of molecules, as well as their development as potential therapeutics, is severely hampered by the lack of robust and general synthetic routes to prepare them. Although there are a number of efficient routes to the synthesis of tricyclanes,³¹⁻³⁴ few have found application in total synthesis. In view of the potential biological interest in this family of compounds, we set out to develop a general and divergent synthetic route to them and in particular to synthesise versatile intermediates that can be used in the preparation of different targets in this family, including functionalised analogues of α -santalene and those with a fourth ring such as longicyclene, **8** and

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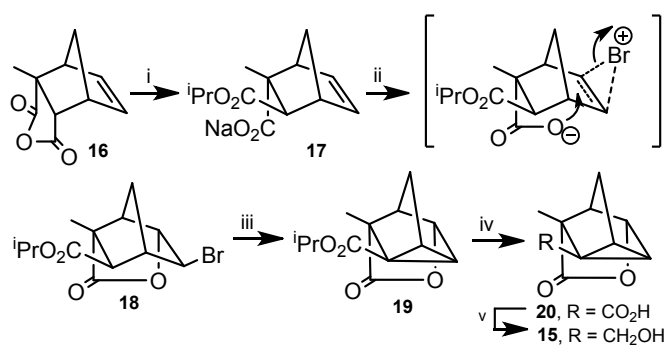
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cyclosativene, **11**. Here we report the first total synthesis of α -ekasantallic acid, **14**,³⁵ a constituent of East Indian sandalwood oil,^{36,37} also known as tricycloekasantallic acid in some literature and preparation of a number of key intermediates, such as **15**, which can be used both in preparation of analogues as well as in total syntheses of other members of this family (Figure 2).

Results and discussion

Commercially available citraconic anhydride underwent an efficient Diels-Alder cycloaddition with cyclopentadiene to afford exclusively the *endo* cycloadduct **16**. Treatment of cycloadduct **16** with sodium isopropoxide, selectively afforded sodium carboxylate salt **17** (Figure 3). The regioselectivity of the acid anhydride ring opening is most likely due to steric factors. The bulky isopropoxide anion avoids attacking the carboxyl function adjacent to the quaternary carbon atom due to the methyl substituent. Furthermore, under these basic reaction conditions, the ester group is epimerised to the less sterically encumbered and hence more thermodynamically favoured *exo* position.



i) *i*-PrONa, *i*-PrOH, rt, 15 h, 92%; ii) Br₂, H₂O, 98%; iii) *tert*-BuOK, THF, 15 h, 65%; iv) 15% Aq. HCl, reflux, 96%; v) BH₃, THF, CH₂Cl₂, rt, 5 h, 89%

Figure 3 Preparation of key intermediate **15**

Treatment of **17** with bromine in water affords bromide **18**. Reaction proceeds *via* formation of a bromonium cation from the less sterically hindered face of the alkene, followed by backside attack of the nucleophilic carboxylate. Treatment of **18** with potassium *tert*-butoxide in tetrahydrofuran resulted in enolisation of the noncyclic ester, followed by intramolecular cyclisation and elimination of potassium bromide to give **19**. We have previously shown that similar carbanion-initiated cyclisations are a facile route to tricyclanes.³¹

It was possible to selectively hydrolyse the non-cyclic ester in **19** under acidic conditions to obtain **20**. Presumably, under acidic conditions, any hydrolysis of the cyclic ester will be followed by facile re-esterification, since the hydroxyl and carboxylic groups are spatially close. Reduction of the carboxylic acid function in **20** with borane afforded the key intermediate alcohol **15** in multigram quantities in 6 steps and 50% overall yield (Figure 3).

Next, alcohol **15** was transformed to iodide **21** which was then treated with lithium aluminium hydride to efficiently afford bisalcohol **22** (Figure 4). In addition to compound **22**, hydride reduction of **21** also afforded compound **23** as a minor byproduct (2% isolated) which is obtained by conjugate addition of a hydride at C-1 to open the cyclopropane ring. Although the yield of this by product is too small for it to be a synthetically useful step, the production of **23** is interesting since chain extension at C10 would lead to β -santalene skeleton.

Our next task was to selectively manipulate one of two hydroxyl groups in compound **22**. However, all our attempts at selective protection of one of two hydroxyl groups in compound **22** were unsuccessful. These included treatment with Boc anhydride, benzoyl chloride and pivaloyl chloride, TBDMSCl, TBDMS-imidazole, and TBDPSCl. Presumably, this is because the primary neopentyl primary alcohol and the secondary alcohol functions have similar steric demand. In order to chemically distinguish the two hydroxyl groups, we converted the bisalcohol **22** to compound **24** by Swern oxidation, with the knowledge that aldehydes react more efficiently than ketones in Wittig type reactions. Gratifyingly, we found that the aldehyde function in compound **24** selectively undergoes Wittig reactions. Thus, treatment of compound **24** with the corresponding Wittig reagent, followed by hydrogenation of the resulting alkene afforded 5-keto- α -ekasantallic acid ethyl ester, **25**. The reduction of the 5-keto group was achieved *via* the transformation to the thione **26**, using Lawesson's reagent, followed by reduction using (NiCl₂/NaBH₄) to afford **27**. The hydrolysis of **27** produced α -ekasantallic acid, **14** (Figure 4). This represents the first total synthesis of (\pm)- α -ekasantallic acid, **14**. Furthermore, compound **27** is a known precursor in the total synthesis of α -santalene,³⁸ therefore this synthetic route also represents a formal synthesis of **1**.

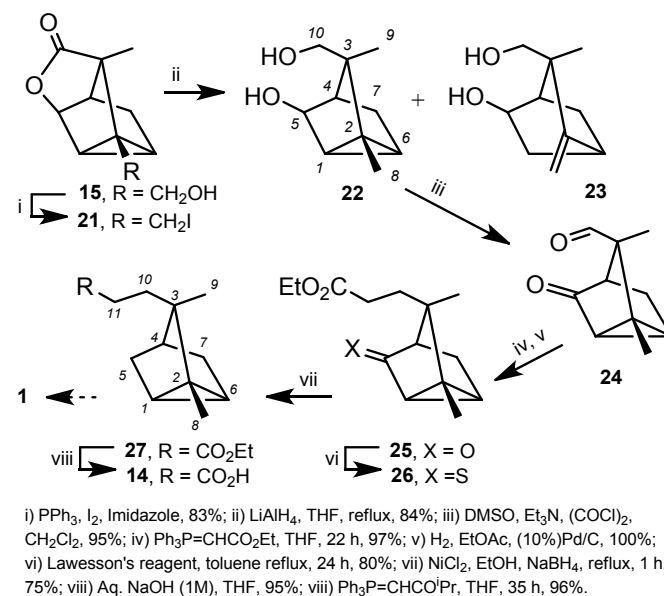


Figure 4 Preparation of (\pm)- α -ekasantallic acid, **14**.

Conclusions

In summary, we report the first total synthesis of (\pm)- α -ekasantalic acid, an unusual sesquiterpenoid containing a tricyclo[2.2.1.0^{2,6}]heptane (tricyclane) ring. The methodology we have developed, uses intermediates in which C5 bears functionality meaning that it can be utilised in the construction of a fourth ring, as present in, for example, longicyclene, **8** and cyclosativene, **11**. Further work towards the total synthesis of these natural products is currently underway in our group. In addition, we are also investigating the biological activity of these compounds and their analogues and will report our results in due course.

Experimental

Synthetic procedures and full characterisation data are provided in the supporting information.

Conflicts of interest

There are no conflicts of interest to declare.

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