Tetrahedron Letters,Vol.30,No.31,pp 4045-4048,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

An Intramolecular Cycloaddition-Sigmatropic Rearrangement Approach to (±) Gascardic Acid

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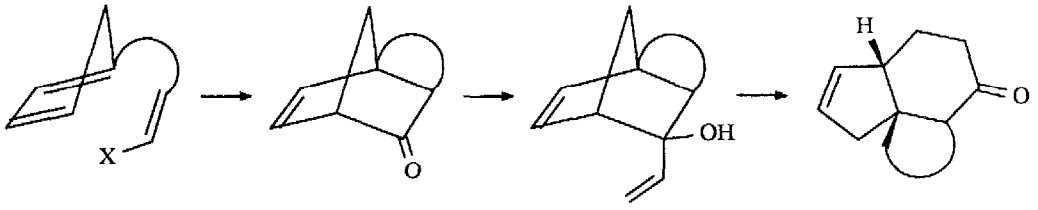
Abstract: A general intramolecular Diels-Alder:anionic oxy-Cope strategy for the synthesis of tricyclic skeletons and its application to the preparation of the gascardic acid precursor **12** is described. *In situ* generation of the appropriate cyclopentadiene **5** by isomerization (Et_3N) afforded the [4+2] adduct directly or with $EtAlCl_2$ as catalyst. The requisite potassium salt of the 1,5 diene **10** rearranged at 67°C to the fused ring ketone **11**. Selective allylic oxidation and reduction provided **12**.

The sesterterpene gascardic acid (**13**)[1] possesses a unique tricyclo[7.5.$0^{1,7}$.$0^{1,11}$]tetradecane skeleton whose structure was established *via* total synthesis[2] and X-ray diffraction.[3] At present, this fused arrangement of five, six and seven membered rings has not been encountered elsewhere, although this structure shares with other angular triquinane natural products, such as subergorgic acid[4] and retigeranic acid[5], a related spiro-fused tricyclic nucleus. There is considerable current interest in the intramolecular Diels-Alder reaction and it has been applied to a number of natural product syntheses with notable success.[6] Similarly, [3,3] sigmatropic rearrangements, particularly of the oxy-Cope variety, have recently received increased attention as versatile construction tools.[7] In principle, a general, stereocontrolled route to many multicyclic skeletons is available from a combination of these pericyclic transformations *via* an intramolecular Diels-Alder:anionic oxy-Cope rearrangement strategy. As illustrated below, the length of the side chain may be varied and the resulting cyclohexanone contracted or expanded as required. We wish to report the successful application of this strategy to the synthesis of the gascardic acid intermediate **12**, in which the key ring junctions and substituents have the correct relative stereochemistry.



The keto-enol ether **1** was derived from 2-methyl-1,3-cyclopentanedione upon treatment with

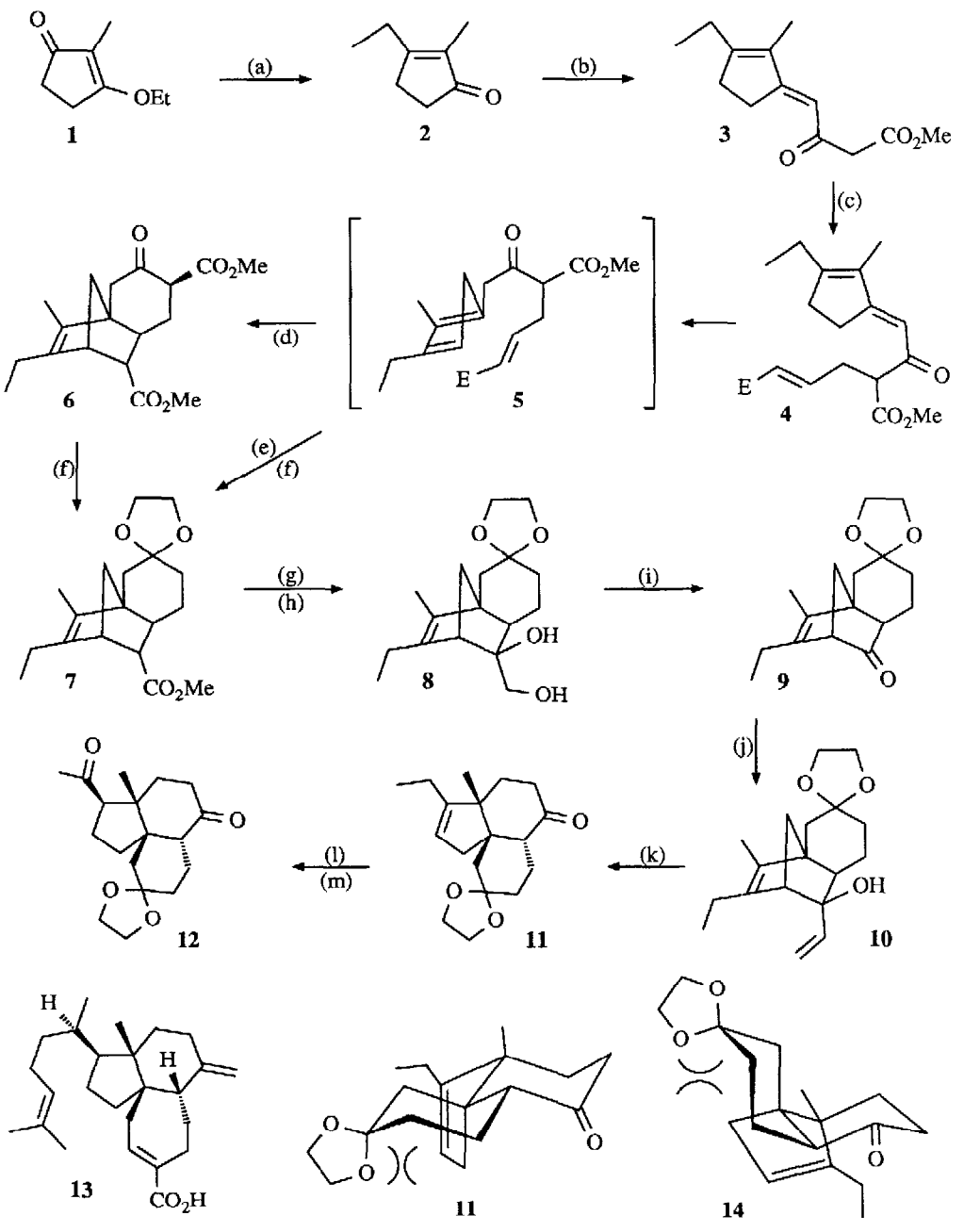
p-toluenesulfonic acid, molecular sieves, and ethanol in refluxing benzene (90%).[8] Ethyllithium generated *in situ* in an ultrasonic bath[9] from bromoethane and Li/Na alloy was condensed with **1** and chromatography of the resulting alcohol gave the cyclopentenone **2** (98%) directly. The dianion derived from methyl acetoacetate,[10] by sequential treatment with sodium hydride and *n*-butyllithium, was added to this cyclopentenone and dehydration of the resulting alcohol effected with 3M HCl to afford the dienone-ester **3**. This material was a single stereoisomer, formed as a consequence of the nonbonded interactions between the ring vinyl methyl function and carbonyl substituent that are avoided in the E-olefin. Alkylation of this keto-ester with methyl 4-bromocrotonate provided the triene-diester **4**.

The requisite Diels-Alder precursor **5** was generated *in situ* from **4**. Treatment of **4** with $EtAlCl_2$ in dichloromethane at room temperature (21^0 C) catalyzed the cycloaddition with a high level of stereocontrol to give the single isomer **6** in modest yield (30%). This adds to the growing list of examples where alkylaluminum halides are the most satisfactory catalysts for effective control of intramolecular [4 + 2] cycloadditions.[11] In principle, several different cyclopentadiene adducts might be envisaged but these alternative adducts are strained due to Bredt's rule violation, etc. Thus in practice, as expected, only the tricyclo[6.2.1.$0^{1,6}$]undecene nucleus was formed.[8] Direct cyclization was also effected, in refluxing toluene containing triethylamine, to a mixture of stereoisomers (100%). This material, which consisted of keto-ester epimers (~1:1), and *endo*/exo ester isomers (5:1.5), was used directly in subsequent transformations. Selective hydrolysis and decarboxylation of the α-ester was effected with lithium chloride in aqueous dimethyl sulfoxide and the resulting cyclohexanone protected as its ethylene ketal to afford the *endo* ester **7** in which the adjacent cyclohexane bond was *exo*.

Two different approaches to the tricyclic 1,5-diene **10** were examined. The ester enolate of **7** was generated at -78°C with lithium diisopropylamide (LDA) and quenched with oxygen to afford the hydroxy ester as a single isomer. Reduction of the methyl ester with $LiAlH_4$ gave the diol **8**. It had been anticipated that the alcohol **10** could be prepared directly by oxidation of the primary alcohol followed by Wittig reaction on the resulting aldehyde. The desired oxidation was accomplished under Swern conditions[12] but unfortunately this hydroxy-aldehyde was very unstable and rendered this route impractical. Consequently, the diol **8** was converted to the ketone **9** by periodate oxidation. In spite of the *exo* orientation of the adjacent cyclohexane ring, the carbonyl was attacked preferentially from the top face with vinyl magnesium bromide to give a 3:1 ratio of *endo* and *exo* alcohols. Conditions to improve this ratio, using a variety of Lewis acids ($CdCl_2$, $ZnCl_2$, $TiCl_4$, $EtAlCl_2$, Et_2AlCl, etc.), were investigated with a view to preferentially complexing the *exo* surface, but the ratio did not change significantly. However, it should be possible to invert the stereochemistry of the undesired isomer to afford **10**, using the [2,3] sulfoxide rearrangement sequence we have developed,[13] although at present this has not been investigated.

Previous studies[14] have established the significant acceleration induced by potassium salts in anionic oxy-Cope rearrangements. Thus, as anticipated, the potassium salt of **10** underwent smooth sigmatropic rearrangement in refluxing THF to the tricyclic ketone **11** in 67% isolated yield. Our previous studies[8] indicated that the cycloheptane ring could not be formed directly in the Diels-Alder step, and this implied that epimerization during the Cope rearrangement step might not be as selective as desired, in spite of the fact that the *trans* ring junction is strongly favored in the cycloheptane series.[2] (The *exo* cyclohexane bond in **10** must be isomerized to generate the natural product stereochemistry present in **11**.) The initial product was a 1:1 mixture of the *trans* and *cis* cyclohexanones **11** and **14**. The latter compound **14** was recycled by isolation and epimerization with sodium methoxide but here also a 1:1 mixture of **11** and its C-6 epimer were obtained. This ratio is a consequence of the very similar nonbonded interactions that are present in each isomer as illustrated.

Molecular models indicated that the cyclopentene ring methylene group in **11** is relatively hindered, compared to the side chain ethyl group, due to the juxtaposition of the oxygen ketal. Thus allylic oxidation with



Reagents (a) EtBr, ether, Li/Na,))), 10^0 C, 1 h, 98%; (b) $CH_3COCH_2COOCH_3$, NaH, THF, 0^0 - 60^0 C, 20 min; BuLi, 0^0 C, 10 min; **2**, 0^0 C, 20 min; 10% aq. HCl, 21^0 C, 1 h, 64%; (c) KH, THF, 0^0 - 21^0 C, 20 min; $BrCH_2CH{=}CHCOOCH_3$, 21^0 C, 2 h, 64%; (d) $EtAlCl_2$, CH_2Cl_2 21^0 C, 16 h, 30%; (e) Et_3N, MeC_6H_5, 110^0, 72 h, 100%; (f) LiCl, H_2O, DMSO, 160^0 C, 1 h, 75%; $HOCH_2CH_2OH$, $MeC_6H_4SO_3H$, C_6H_6, 80^0 C, 6 h, 43% from **4**; (g) iPr_2NH, *n*BuLi, THF, 0^0 C, 10 min; **7**, -78^0 C, 1 h; O_2, -78^0 C, 2 h, 43%; (h) $LiAlH_4$, ether/CH_2Cl_2 1:1, 0^0 - 21^0 C, 30 min; (i) $HIO_4.2H_2O$, ether/CH_2Cl_2 1:1, 0^0 -21^0 C, 1 h, 30% from **7**; (j) $CH_2{=}CH_2MgBr$, 21^0 C, 30 min, 84% 1:4 *exo*/*endo* alcohol; (k) KH, I_2, THF, 21^0 C, 10 min; **10**, 21^0 - 67^0 C, 30 min, 67% 1:1; (l) SeO_2, dioxane,80^0 C, 4 h; PCC, NaOAc, 4A sieves, CH_2Cl_2, 0^0 - 21^0 C, 1h, 49%; (m) Li, $NH_2CH_2CH_2NH_2$, dioxane, *t*-BuOH, 30 min; PCC, NaOAc, 4A sieves, CH_2Cl_2, 0^0 - 21^0 C, 1h, 24%.

selenium dioxide followed by oxidation of the secondary alcohol with pyridinium chlorochromate (PCC) afforded the conjugated methyl ketone rather than the corresponding cyclopentenone. Treatment of this unsaturated ketone with lithium/ethylene diamine followed by PCC to correct some reduction of the carbonyl function provided the tricyclic triketone **12**. In view of the concave nature of the skeleton dissolving metal reduction should generate the methyl ketone with a *cis* orientation relative to the bridgehead methyl group. This was confirmed by ^{1}H nmr NOE difference spectra which displayed strong (20-27%) signal enhancements for the methyl ketone (δ 2.19) and tertiary methyl (δ 0.74) signals consistent with stereochemistry illustrated. Other spectral data (^{1}H nmr, ^{13}C nmr, IR, MS) were also in accord with these structures.

In conclusion, as illustrated by the synthesis of **12**, this intramolecular cycloaddition-[3,3] sigmatropic rearrangement strategy provides a general entry to diverse multicyclic skeletons contained in natural products such as gascardic acid.

Acknowledgments: We are grateful to Memorial University of Newfoundland (where this project was initiated), the University of Ottawa and the Natural Sciences and Engineering Research Council of Canada for financial support of this research and to H. Dettman for nmr spectra.

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(Received in USA 3 May 1989)