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A Diene Transmissive Diels–Alder Strategy for Oxygenated Nor-Steroid and Triterpenoid Skeletons†

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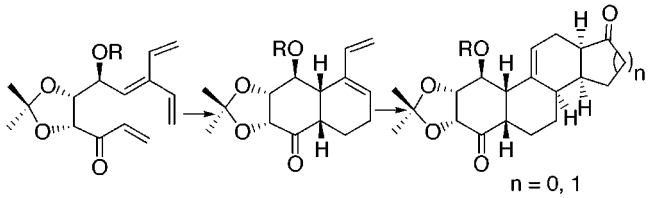
ABSTRACT



A diene transmissive cycloaddition strategy for the synthesis of tetracyclic skeletons is described. Initially both L-gulonolactone and L-arabinose were converted independently to related acetal aldehydes 13 and 14. A pentadienyl indium reagent supplied the triene unit for 16. The *cis*-isopropylidene acetal controlled the initial intramolecular [4 + 2] cycloaddition to the decalin 21, and a second (tandem) intermolecular cyclization afforded highly oxygenated nor-steroid and triterpenoid skeletons as chiral nonracemic compounds.

The synthesis and study of triterpenes and steroids continues to be a topic of widespread interest. In part, this is a consequence of the novel biological properties some of these compounds display and the importance of steroids in mammalian systems. For example, compounds from *Ganoderma* species, such as ganoderic acid D (**1**, Figure 1) and its relatives, possess anticancer, antihypertension, and immuno-modulating effects.[1] An Antarctic starfish has supplied the interesting polyhydroxylated steroid **2**.[2] Similarly, the invertebrate molting hormone α-ecdysone[3] possesses both a *cis*-1,2-diol functionality in the A ring and a rare *cis*-fused ring junction in the A−B decalin component.

A general strategy, for the basic ring systems of these highly oxygenated skeletons is outlined in Scheme 1. This route is based on an extension of our synthetic investigations into tether-controlled Diels−Alder cycloadditions,[4] coupled with the recent development of procedures to introduce the triene unit from pentadienyl indium condensations.[5] This approach should allow the rapid construction of various tetracyclic skeletons in an enantioselective manner. Recent

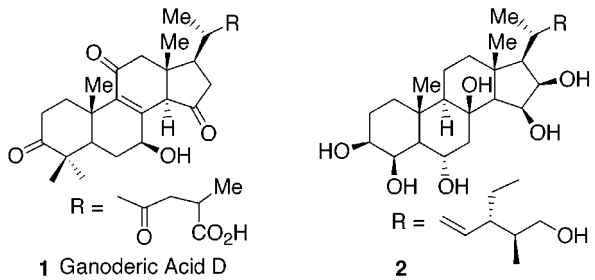


Figure 1. Highly Oxygenated Triterpenoid and Steroid Systems

† This paper is dedicated to Professor Stephen Hanessian on the occasion of his 65th birthday. Presented with respect and gratitude for his contributions to organic chemistry.

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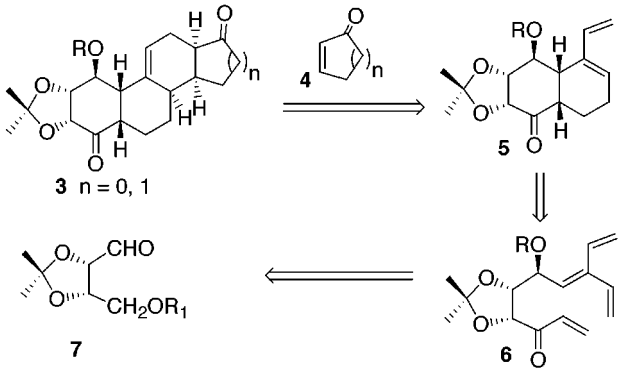
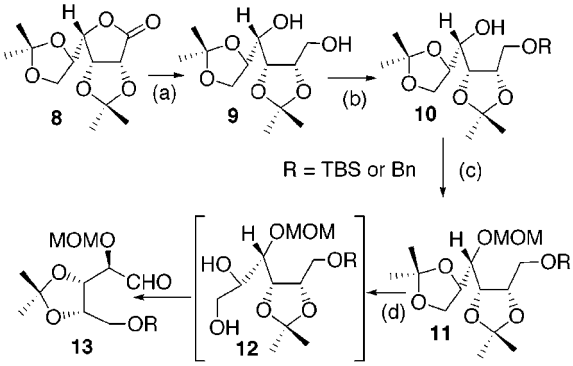
Scheme 1. Retrosynthetic Strategy for Nor-Steroids and Triterpenoids



studies have established that a *cis*-isopropylidene acetal[6] is superior to the *trans* isomer[7] for facilitating intramolecular cycloadditions. The acetal unit in **7** will direct and control the stereochemical outcome of the desired cyclization to decalin **5** from the precursor **6**. Tricyclic ketone **5** is suitably functionalized for a second cycloaddition to afford compounds with the general structure **3**.

Initially, the desired *cis* acetal substrate **13** (related to aldehyde **7**) was synthesized from L-gulonolactone via bis-acetal **8**[8] according to Scheme 2. Thus, hydride reduction of

Scheme 2. Synthesis of Aldehyde **13**

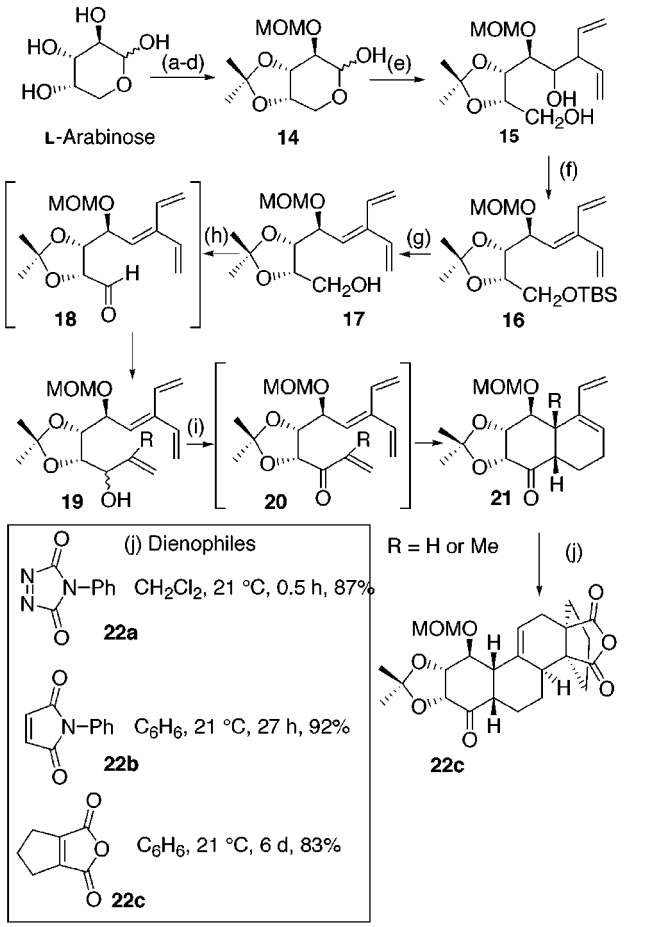


(a) $LiAlH_4$, THF, 95%; (b) Et_3N, DMAP, TBSCl or BnBr, KH; (c) MOMCl, NaH, THF, 82%; (d) 3 eq. H_5IO_6, Et_2O, 46%, R = Bn.

8 afforded diol **9**. Selective protection of the primary alcohol as a *tert*-butyldimethylsilyl ether gave compound **10** (R = TBS) in which the remaining secondary hydroxyl group was protected as a methoxymethyl ether to provide **11** (R = TBS). Treatment of this bis-acetonide with periodic acid did not effect the selective acetonide hydrolysis and oxidative cleavage desired. The best yield of **13** (R = TBS) was 26%.[9] Similarly, exposure to acetic acid in a separate step did not provide reproducible results nor the required discrimination due to concomitant hydrolysis of the silyl ether. Thus the silyl group in **11** was replaced with a benzyl ether by initial treatment with tetra-*n*-butylammonium fluoride to generate the primary alcohol related to **11** (R = H). This was followed by the reaction of the potassium alkoxide with benzyl bromide to afford **11** (R = Bn). In this instance periodic acid reacted with **11** (R = Bn) to selectively hydrolyze the least substituted acetonide and oxidize the resulting diol **12** in situ to generate aldehyde **13** (R = Bn) in a slightly improved yield of 46%.

A more expeditious route to the required aldehyde related to **13** employed hemiacetal **14** as outlined in Scheme 3. This

Scheme 3. Synthesis of Oxygenated Tetracyclic Skeletons from L-Arabinose



(a) BnOH, HCl, 21 °C, 16 h, 88%; (b) Me_2CO, $CuSO_4$, H_2SO_4, 21 °C, 20 h, 75%; (c) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 96%; (d) Na/NH_3, Et_2O, 97%; (e) $In_{(s)}$, $BrCH_2CH{=}CHCH{=}CH_2$, DMF, 21 °C, 96%; (f) Et_3N, CH_2Cl_2, DMAP, TBSCl; Ph_3P, DEAD, C_6H_6, 80 °C, 90%; (g) Bu_4NF, THF, 0 °C, 99%; (h) 1.5 eq. $(COCl)_2$, CH_2Cl_2, 3 eq. DMSO, -78 °C, 7 eq. Et_3N,0 °C; 4 eq. $BrMgCH{=}CH_2$, -78-0 °C, 93%; (i) 1.5 eq. $(COCl)_2$, CH_2Cl_2, 3 eq. DMSO, -78 °C, 7 eq. Et_3N, 78%

sequence commenced with L-arabinose and involved the protection−deprotection protocol illustrated. Thus, the anomeric hydroxyl group was protected as its benzyl ether and the *cis*-diol was selectively protected as an acetonide.[10] The remaining hydroxyl group was converted to its methoxymethyl ether, and the benzyl ether was cleaved with sodium in liquid ammonia to afford **14**.

Addition of pentadienyl indium to hemiacetal **14** afforded 1,4-diene **15** as a 1:1 mixture of diastereomers in 96% yield.[5] The primary alcohol was selectively protected as a silyl ether, and the secondary alcohol was eliminated under either Mitsunobu type conditions or with Martin's sulfurane to give triene **16** in yields of 90% and 99%, respectively. Material closely related to alcohol **15** was also synthesized from aldehyde **13** (R = Bn) by a parallel diene addition. Fluoride-induced removal of the primary silyl group in **16** released alcohol **17**, which was oxidized under Swern conditions to give aldehyde **18**. This compound was reacted directly with vinylmagnesium bromide to generate allylic alcohol **19**. A second Swern oxidation formed ketone **20** in situ which cyclized spontaneously (without isolation of this enone) at room temperature (21 °C) to afford adduct **21** (R = H, 78%). The bridgehead methyl substituent (C-19) was introduced by reacting aldehyde **18** with 2-propenylmagnesium bromide. Oxidation of the resulting alcohol **19** (R = Me) under Swern conditions afforded ketone **20** (R = Me). In the same manner as above, the ketone was not isolated and cyclized after 1 h at 0 °C to provide adduct **21** (R = Me) in 76% yield.

This *cis* isopropylidene acetal system cyclized more readily than a closely related *trans* isomer.[6,7] Thus epimerization of an acetal center improved the efficiency of the reaction but led to the same stereochemical result.

The *endo* transition state **23** is preferred, in which the tether adopts a boatlike conformation to accommodate the adjacent acetonide oxygen bond and neighboring ether in an equatorial relationship. This orientation places the diene and dienophile in close proximity for facile cyclization (Figure 2). The

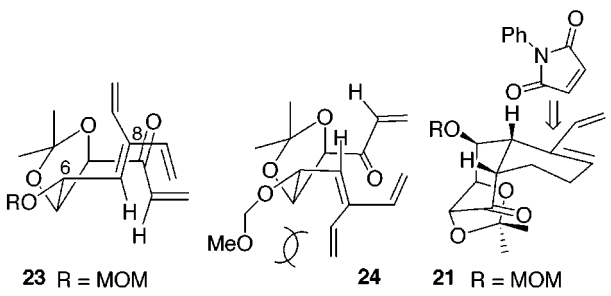


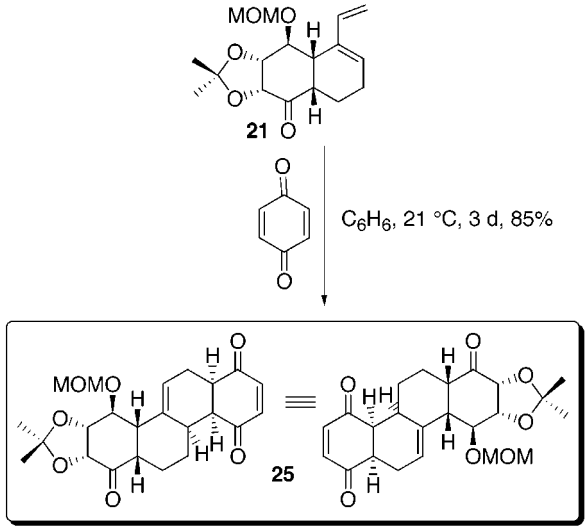
Figure 2. Cycloaddition Transition States

significant nonbonded interactions, between the vinyl and methoxymethyl substituents, evident in other transition states such as **24**, are thus avoided.

The decalin diene **21** containing the A−B framework is now suitably functionalized for a second (tandem[11]) [4 + 2] cycloaddition. A variety of tetracyclic steroidal type systems related to **22** were produced, with high stereocontrol in yields of 83−92%, depending upon the cyclic dienophile selected (box, Scheme 3). These dienophiles added from the most accessible convex face of **21** in an *endo* orientation as illustrated in Figure 2.

In a parallel fashion, benzoquinone added selectively to **21** (Scheme 4) from the top face to form the highly

Scheme 4. Cycloaddition to Nor-Triterpenoid **23**



oxygenated nor-triterpenoid **25** in 85% yield. A single-crystal X-ray analysis of **25** confirmed the stereochemical assignments illustrated. It is obvious that considerable functional group manipulation of these ring systems is possible. In addition, the six-membered rings in **25** bearing carbonyl groups may be viewed as either the A or the D ring component depending upon the synthetic objective. Furthermore, the ring fusion in these adducts may be adjusted at several of the different bridgehead positions due to the presence of the adjacent ketone or vinyl functionality.

In conclusion, we have developed a versatile tandem Diels−Alder strategy, based on acetal and triene building blocks, for the rapid assembly of highly oxygenated, nor-methyl triterpenoid and steroid type skeletons in an enantiospecific manner. Additional investigations are under development and will be reported in due course.

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