Facile retro-cycloaddition of adducts derived from steroidal 5,7-diene and 4-phenyl-1,2,4-triazoline-3,5-dione by diisobutylaluminium hydride

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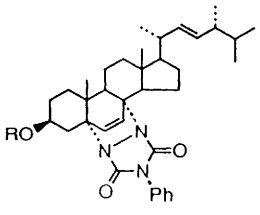
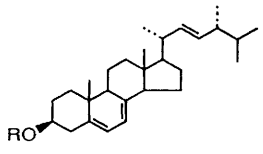
Facile retro-cycloaddition of adducts derived from a steroidal 5,7-diene and 4-phenyl-1,2,4-triazoline-3,5-dione was achieved by diisobutylaluminium hydride under mild conditions.

Dienes readily undergo cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to give adducts in high yield.[1] In such a way, steroidal 5,7-dienes have been protected for synthetic studies,[2,3] although the retro-cycloaddition necessary to remove the PTAD protecting group requires relatively drastic conditions: $LiAlH_4$–THF, reflux;[2] K_2CO_3–DMSO or DMF at 120 °C;[4] tetramethylguanidine or 2,4,6-trimethylpyridine, reflux;[5] KOH–EtOH.[6] An improved procedure has, however, been reported recently.[7] During synthetic studies on vitamin D analogues, we found that the retro-cycloaddition can be facilitated under mild conditions, by the use of diisobutylaluminium hydride (DIBAL-H), and here report the scope of this novel procedure employing ergosterol derivatives as substrates.

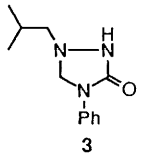
First, the conditions were optimized for the adduct **1a**. In order to go to completion, use of 4 equiv. of DIBAL-H at 0 °C in toluene was necessary. With less DIBAL-H or for reactions



1 a R=TBS
b R=THP
c R=MOM
d R=Ac
e R=H



2 a R=TBS
b R=THP
c R=MOM
d R=H



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conducted at the lower temperature, the yield decreased dramatically. Although toluene was the solvent of choice, CH_2Cl_2 gave only slightly lower yields; much lower yields were obtained with ether as solvent. Under optimized conditions, the reaction proceeded to completion almost instantaneously to give along with **2a**, a triazolidinone **3**[8] (25%), derived from the urazole moiety. Interestingly, this result is different from that of the procedure using $LiAlH_4$, with which the products obtained were aniline, *N*-methylaniline and *N*,*N*-dimethylaniline.[2] Although this result suggested that DIBAL-H operates as a reducing agent in this reaction, the possibility cannot be ruled out that it acts as a Lewis acid catalyst. In this context, the other reducing agents which can reduce amides (lithium triethylboranuide and borane–methyl sulfide complex) and Lewis acids

Table 1 Retro-cycloaddition of ergosterol derivatives by DIBAL-H

Entry	Substrate[a]	Product[b]	DIBAL-H (equiv.)[c]	Yield (%)
1	**1a**	**2a**	4	87
2	**1b**	**2b**	4	91
3	**1c**	**2c**	4	94
4	**1d**	**2d**	10	70
5	**1e**	**2d**	20	51
6	**4a**	**5a**	20	81
7	**4b**	**5b**	8	80
8	**4c**	**5c**	6	68

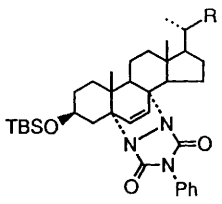
[a] These substrates were prepared according to the procedures reported in the literature. [b] The spectral data of the products were in accord with the assigned structures or identical with those reported in the literature. [c] All reactions were conducted at 0 °C in toluene for 10 min.

($AlMe_3$, Me_2AlCl and $EtAlCl_2$)† were employed, but none of them promoted the retro-cycloaddition. Additionally, this procedure was ineffective for the adducts from other typical dienophiles; for example, treatment of the adducts from 2,3-dimethylbuta-1,3-diene and dimethyl acetylenedicarboxylate or *N*-phenylmaleimide with DIBAL-H under the optimized conditions gave the corresponding reduction products in high yield but no diene.

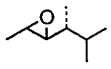
The effects of protective groups on 3-OH and functional groups in the side-chain were examined next and the results are summarized in Table 1. MOM and THP protective groups on 3-OH were as good as, or indeed superior to, TBS; **1b** and **1c** gave the corresponding dienes **2b** and **2c**, respectively, in high yield under the same conditions (entries 2 and 3). The acetyl group in compound **1d** was reduced by DIBAL-H in this procedure, so that 10 equiv. of DIBAL-H was required to obtain ergosterol **2d** from **1d** in good yield (entry 4). However, without protection of the 3-OH, the reaction was sluggish and the yield was much lower than the above cases even with a large excess of DIBAL-H (entry 5). In contrast, the presence of the OH group in the side-chain such as the adduct **4a** hardly affected the yield when 20 equiv. of DIBAL-H was used (entry 6). The epoxide in **4b** was not reduced and remained intact in this procedure (entry 7). The retro-cycloaddition of the nitrile **4c** proceeded well with concomitant reduction of the nitrile to the aldehyde (entry 8). Thus, except for **1e**, the yields obtained were satisfactory and comparable to those of the known procedures.[2–7]

This novel procedure for retro-cycloaddition of the adducts from steroidal 5,7-dienes and PTAD can be conducted under

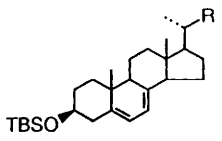
† Treatment of the adducts from steroidal 5,7-dienes and PTAD with BF_3·OEt_2 has been reported to give anthrasteroids *via* oxidative rearrangement.[9]



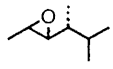
4 a R=CH_2OH

b R= 

c R=CH_2CN



5 a R=CH_2OH

b R= 

c R=CH_2CHO

mild conditions and tolerates a variety of protective and functional groups. Therefore, it should be useful for the synthesis of vitamin D and its derivatives from steroidal precursors.

Experimental

Typical procedure for the retro-cycloaddition (entry 1 in Table 1)

To a stirred solution of **1a** (200 mg, 0.29 mmol) was added DIBAL-H–hexane (1 mol dm^{-3}; 1.2 cm^3, 1.2 mmol, 4 equiv.) at 0 °C and the mixture stirred at 0 °C for 10 min under argon atmosphere. The reaction was quenched by the addition of aq. NH_4Cl to the mixture which was then dried ($MgSO_4$) and evaporated to give a crystalline crude product. This was purified by silica gel flash chromatography (6 g, 2–20% AcOEt–hexane) to give **2a** (130 mg, 87%) and **3** (16 mg, 25%).

Compound **2a**: colourless needles, mp 106–107 °C (recrystallized from AcOEt–hexane, 1:4); δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.05 (s, 6 H), 0.61 (s, 3 H), 0.80 (d, 3 H, *J* 6.4), 0.82 (d, 3 H, *J* 6.2), 0.87 (s, 9 H), 0.90 (d, 3 H, *J* 7.0), 0.92 (s, 3 H), 1.01 (d, 3 H, *J* 6.7), 3.57 (ddt, 1 H, *J* 4.3, 11.9, 6.7), 5.15 (dd, 1 H, *J* 7.3, 15.3), 5.21 (dd, 1 H, *J* 7.0, 15.3), 5.36 (dt, 1 H, *J* 5.5, 2.7) and 5.53 (d, 1 H, *J* 5.5); ν_{max}(Nujol)/cm^{-1} 1254 and 1094; *m/z* 510 (M^+) and 378 (M^+ – TBSOH) (Found: M^+, 510.4257. $C_{34}H_{58}OSi$ requires *M*, 510.4257).

Compound **3**: colourless oil; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.97 (d, 6 H, *J* 6.7), 1.80 (tqq, 1 H, *J* 7.0, 6.7, 6.7), 2.65 (d, 2 H, *J* 7.0), 4.78 (s, 2 H), 6.25 (s, 1 H), 7.11 (tt, 1 H, *J* 1.2, 7.2), 7.37 (tt, 2 H, *J* 1.2, 7.2) and 7.43 (dq, 2 H, *J* 7.2, 1.2); δ_c(100 MHz; $CDCl_3$; Me_4Si) 20.5 (d), 26.4 (q), 68.0 (t), 71.5 (t), 117.7 (d), 123.5 (d), 129.0 (d), 138.0 (s), 158.5 (s); ν_{max}(neat)/cm^{-1} 1713, 1601 and 1505; *m/z* 219 (M^+), 176 (M^+ – Pr^i) and 162 (M^+ – Bu^i) (Found: M^+, 219.1369. $C_{12}H_{17}N_3$ requires *M*, 219.1380).

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8 The structure of this compound was unambiguously determined by spectral analyses, especially by 2D-NMR (COSY, HMQC and HMBC).

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