Convenient Formal Synthesis of (+)-Grandisol through Lewis Acid Promoted Enantioselective Pinacolic Rearrangement

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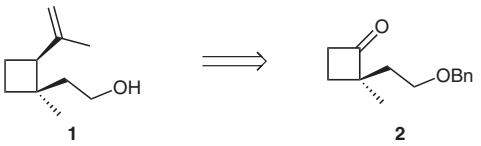
Abstract: The titanium-mediated cyclopropanation of an easily prepared chiral a-siloxylactone leads efficiently to an enantiomerically pure cyclopropanol derivative. The trimethylsilyl trifluoromethane sulfonate induced pinacol rearrangement allows high level of chirality transfer into a cyclobutanone, which is a useful intermediate in the total synthesis of (+)-grandisol.

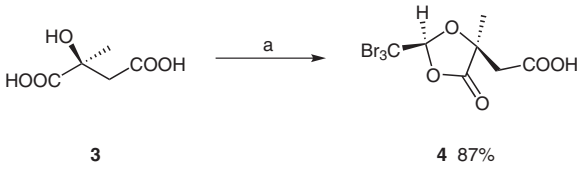
Key words: antifugal agents, aldol reactions, rearrangements, ring expansion, ketones

Grandisol (**1**) is a natural monoterpenic pheromone isolated in 1967[1] presenting two chiral centers on a cyclobutane ring. Used as the major component of grandlure to protect cotton crops against various insects, grandisol is a sex attractant of the cotton boll weevil (*anthonomis grandis*). Over the years, various research groups[2] have tried to prepare grandisol (**1**; Scheme 1) in enantiomerically pure form, but, for the most part, these syntheses require a large number of steps, sometimes difficult, and the enantiomeric excess can be disappointing.



Scheme 1 Retrosynthetic synthesis of (+)-(1*R*,2*S*)-grandisol

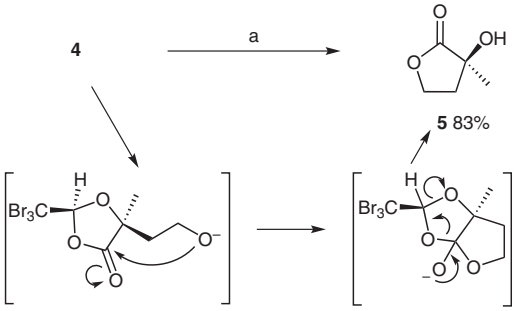
Retrosynthetically, the chiral cyclobutanone **2** constitutes an efficient precursor for the enantioselective synthesis of (+)-grandisol (Scheme 1). Indeed, in our previous work, we showed that the racemic cyclobutanone **2** can be transformed into (±)-grandisol.[3] Thus, access to enantiomerically pure cyclobutanone **2** would provide a formal synthesis of (+)-grandisol (**1**). We decided to apply the method described by Cha[4] for the preparation of optically enriched 2-substituted cyclobutanones. Thus acidic condensation of the commercially available (*S*)-citramalic acid (**3**) with tribromoacetaldehyde[5] afforded the corresponding acid as a unique diastereomer **4** (Scheme 2). The



Scheme 2 *Reagents and conditions*: (a) bromal (1.2 equiv), H_2SO_4–AcOH (1:1, 0.3 mL/mmol), 0 °C, 2 h.

relative configuration was determined by NOESY two-dimensional NMR experiments.

Reduction of acid **4** using borane dimethylsulfide complex[6] directly afforded without basic treatment[7] the pure α-hydroxylactone **5**[8] according to the mechanism depicted in the Scheme 3.



Scheme 3 *Reagents and conditions*: (a) 2 M $BH_3{\cdot}SMe_2$ in THF (0.5 equiv), THF, –10 °C, 1 h, then MeOH, 20 °C, overnight.

Attempts to perform the intermolecular cyclopropanation reaction[9] on the lactone **5** did not lead to the expected cyclopropanol **6**, but returned the lactone practically unchanged, only the isopropyl ester **7** was isolated in very low yield (10%) possibly resulting from the nucleophilic attack of isopropyl anion on the lactone function. Such titanium tetraisopropoxide promoted *trans*-esterification has been previously reported in the Kulinkovich reaction[10] (Scheme 4).

To overcome this problem, the hydroxyl group of the lactone **5** was protected as a silyl ether giving the α-(silyloxy)lactone **8**[8] which successfully underwent the intermolecular cyclopropanation reaction using excess of ethylmagnesium bromide in the presence of titanium tetraisopropoxide. The cyclopropanol **9** was isolated as an enantiomerically pure product in 88% yield (Scheme 5)

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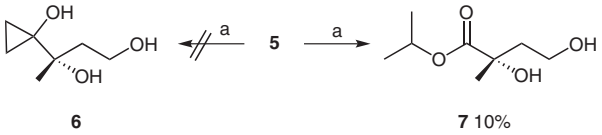
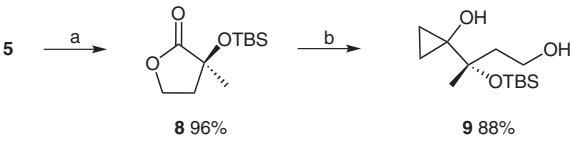


Scheme 4 *Reagents and conditions*: (a) Ti(O*i*-Pr)$_4$ (0.5 equiv), 1.5 M EtMgBr (4 equiv), THF–Et$_2$O (1:1), 0 °C, 4 h.



Scheme 5 *Reagents and conditions*: (a) 2,6-lutidine (0.5 equiv), *tert*-butyldimethylsilyl trifluoroacetate (1.5 equiv), 0–20 °C, 48 h; (b) Ti(O*i*-Pr)$_4$ (0.5 equiv), 1.5 M EtMgBr (4 equiv), THF–Et$_2$O (1:1), 0 °C, 4 h.

and the structure was confirmed by X-ray crystal-structure analysis (Figure 1).[11]

Surprisingly, efforts to induce the pinacol-type rearrangement using BF$_3$ etherate as Lewis acid in dichloromethane furnished not only the cyclobutanone **10** but additionally the chiral dioxolane **11** through an internal cyclization (Scheme 6). Unfortunately, the two products were found to be inseparable by chromatography on silica gel.

To avoid hemiacetal formation, benzylation[12] was carried out on the primary hydroxyl group of the diol **9**[13] to give

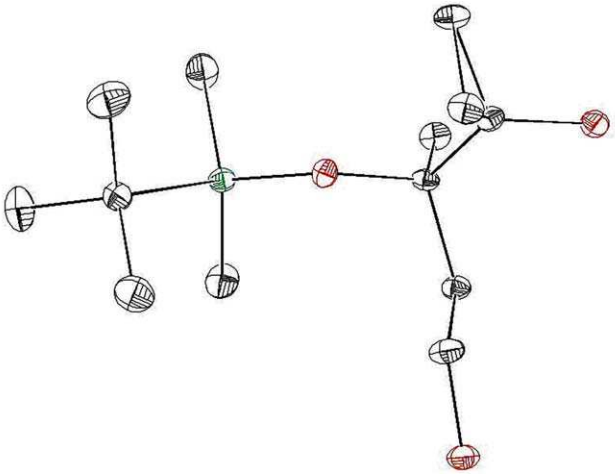
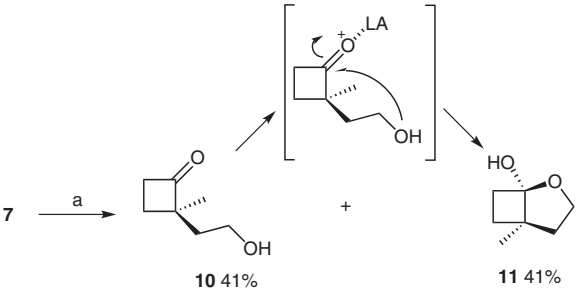


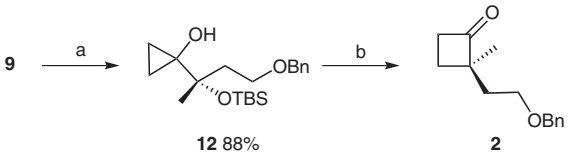
Figure 1 ORTEP plot of X-ray crystal structure of cyclopropanol **9**



Scheme 6 *Reagents and conditions*: (a) BF$_3$·OEt$_2$, –40 °C, CH$_2$Cl$_2$.

the protected cyclopropanol **12**[13] which underwent pinacol rearrangement to yield the desired chiral cyclobutanone **2**.[3] In order to examine the scope of this transformation with a view to optimize enantioselectivity, several attempts were effected in varying Lewis acids and conditions were studied. Thus, a 95% ee was obtained by performing the reaction with *tert*-butyldimethylsilyl trifluoromethane sulfonate in dichloromethane at –78 °C (Table 1).

Table 1 Transformation of Diol **9** into Cyclobutanone **2** via Pinacol Rearrangement of Cyclopropanol **12**[a]



Entry	Lewis acid	Solvent	Temp (°C)	Yield (%)	ee (%)
1	SiO_2	MeOH–CH_2Cl_2	20	97	80
2	BF_3·OEt_2	CH_2Cl_2	–40	95	65
3	BF_3·OEt_2	CH_2Cl_2	–78	91	78
4	BF_3·OEt_2–lutidine	CH_2Cl_2	–78	92	75
5	TBSOTf–lutidine	CH_2Cl_2	–78	89	95
6	TBSOTf–lutidine	pentane	–100	–	–

[a] Reaction conditions: (a) NaH (1 equiv), TBAI (3 equiv), BnBr (1 equiv), 0 °C, then 50 °C, 2 h; (b) Lewis acid.

In conclusion, we have developed a new and concise access to useful chiral intermediate **2**[13] for the efficient preparation of (+)-grandisol. Two key steps allowed efficient access to this compound: firstly, the reduction of a tribromodioxalane by borane dimethyl sulfide complex led to an enantiomerically pure lactone and secondly the remarkable transfer of chirality was induced by the *tert*-butyldimethylsilyl trifluoromethane sulfonate–lutidine couple at low temperature. Finally, starting from commercially available (*R*)-citramalic acid, the same reaction scheme should lead to the other antipode of grandisol.

Acknowledgement

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(7) **Reduction Procedure**: To a solution of [(4*S*)-4-methyl-5-oxo-2-(tribromomethyl)-1,3-dioxolan-4-yl]acetic acid (**4**; 2.64 g, 6.45 mmol) in anhyd THF (15 mL) was added dropwise at –10 °C under argon a solution of borane methyl sulfide complex (1.75 mL, 3.48 mmol, 2 M in THF). After stirring for an additional hour at –10 °C, the reaction mixture was allowed to warm overnight to r.t. The mixture was quenched with MeOH (1 mL) and concentrated under reduced pressure and the resulting oil was diluted in Et_2O (50 mL). The ethereal phase was washed with brine (5 mL) and then dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography to afford pure (3*S*)-dihydro-3-hydroxy-3-methyl-2(3*H*)-furanone (**5**; 0.65 g, 83%); $[\alpha]_D^{20}$ –32.2 (*c* 0.1, $CHCl_3$).

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(11) Crystallographic data for (–)-**9**: $C_{13}H_{28}O_3Si$, M = 260.44, monoclinic, space group *C*2, a = 12.359(5) Å, b = 7.468(5) Å, c = 17.642(5) Å, β = 101.69°, *Z* = 2, *V* = 1594.54 Å^3. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre CCDC as supplementary publication number CCDC 697709. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 IEZ, UK, fax: +44 (1223)336033, e-mail: deposit@ccdc.cam.ac.uk; www.ccdc.cam.ac.uk/data_request/cif.

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(13) Selected data:
1-[(1*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-1-methylpropyl]cyclopropanol (9): colorless needles; mp 65 °C; $[\alpha]_D^{20}$ –12 (*c* 0.1, $CHCl_3$). IR (KBr): 3289, 2957, 1464, 1254 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.94–4.03 (m, 1 H), 3.64–3.78 (m, 1 H), 2.02–2.07 (m, 1 H), 1.70–1.87 (m, 1 H), 1.31 (s, 3 H), 0.82–0.97 (m, 2 H), 0.84 (s, 9 H), 0.59–0.64 (m, 2 H), 0.11 (s, 3 H), 0.07 (s, 3 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 75.3, 60.1, 58.3, 43.0, 41.9, 25.2, 11.4, 8.2, 2.6, 2.3. HRMS (ES, +): *m*/*z* calcd for $C_{13}H_{28}O_3SiNa$: 283.17054; found: 283.17058.
1-[(1*S*)-3-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)-1-methylpropyl]cyclopropanol (12): colorless oil; $[\alpha]_D^{20}$ –34 (*c* 0.05, $CHCl_3$). IR (neat): 3501, 2929, 1454, 1256 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.37 (m, 5 H), 4.54 (Abq, *J* = 3.3 Hz, 2 H), 3.96–4.03 (m, 1 H), 3.71–3.78 (m, 1 H), 3.69 (s, 1 H), 1.99–2.15 (m, 1 H), 1.89–1.97 (m, 1 H), 1.27 (s, 3 H), 0.76–0.93 (m, 2 H), 0.87 (s, 9 H), 0.59–0.63 (m, 2 H), 0.10 (s, 3 H), 0.06 (s, 3 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 129.2, 128.4, 128.2, 126.9, 78.2, 58.6, 40.0, 37.3, 29.2, 26.2, 25.6, 9.4, 7.5, 2.8, 2.3. HRMS (ES, +): *m*/*z* calcd for $C_{19}H_{34}O_3SiNa$: 373.21749; found: 373.21712.
(2*R*)-2-(2-Benzyloxyethyl)-2-methylcyclobutanone (2): colorless oil; $[\alpha]_D^{24}$ +42 (*c* 0.1, $CHCl_3$). IR (neat): 1765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 4.43 (Abq, *J* = 11.7 Hz, 2 H), 3.56 (t, *J* = 6.3 Hz, 2 H), 2.98 (t, *J* = 6.3 Hz, 2 H), 1.93–2.01 (m, 2 H), 1.86 (s, 3 H), 1.64–1.79 (m, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 214.8, 138.1, 128.2, 127.4, 127.3, 72.8, 66.7, 62.2, 42.3, 35.3, 23.9, 21.3. MS (EI): *m*/*z* (%) = 218 (1) [M$^+$], 127 (12), 97 (11), 91 (100), 41 (38).