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A *C-B-A-D* Approach to Brassinosteroids; Obtention of a *A-B-C* Ring System Precursor

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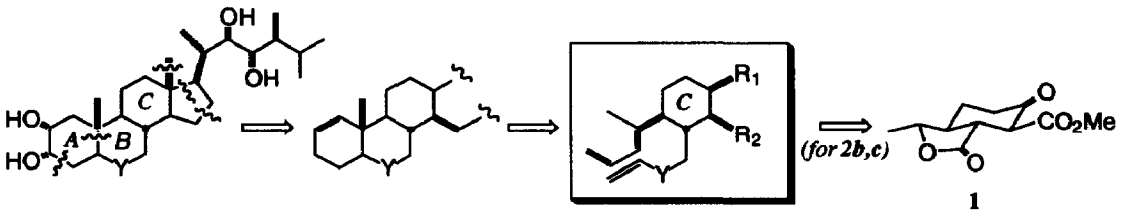
Abstract: *Attempted conversion of the keto group of derivatives of trans-2-acetylcyclohexanemethanol to a butadienyl moiety proved unfeasible by using Wittig-type reagents. Olefination could be achieved however by condensing the parent methyl (or ethyl) trans-2-acetylcyclohexanecarboxylate with the lithio derivative of O-tetrahydropyranylated propargyl alcohol and reducing the resulting lactones by $LiAlH_4$.*

As part of a planned total synthesis of brassinosteroids, we prepared a ketoester, i.e. **1**, featuring the *C*-ring of the steroidal framework.[1] As shown below, the next requirement was to convert this lactonic product into a cyclohexane derivative appended to both a diene and a dienophilic residues (i.e. **2**); intramolecular Diels-Alder (IMDA) reaction of this unsaturated compound should provide the expected *A-B-C* ring system. A convenient access to trienes **2** is described herein.



Brassinolide, Y=C(O)-O-
Castasterone, Y=CO

1

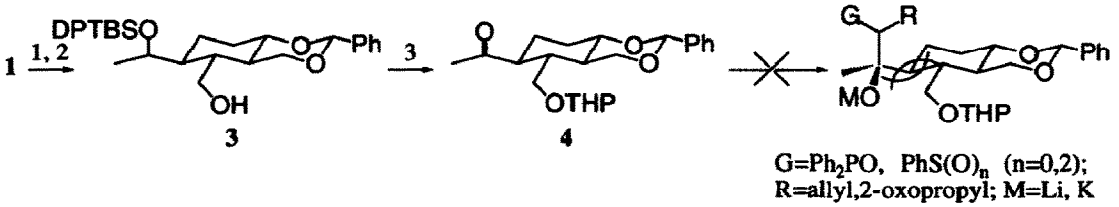
2a, R_1=R_2=H; Y=CO
2b, R_1,R_2=OCH(β-Ph)-OCH_2; Y=CO
2c, R_1,R_2=OCH(β-Ph)-OCH_2; Y=C(O)-O-

The presence in **1** of three carbonyl groups rendered necessary some preparatory protections; only the lactone moiety had to be engaged in the planned transformation.

Methanolysis of lactone **1** catalysed by CSA, followed by silylation of the resulting hydroxyester by DPTBSCl and reduction by LAH afforded a triol whom condensation with benzaldehyde dimethyl acetal in CH_2Cl_2 gave the acetal **3**. Pyranylation of the primary hydroxyl group (DHP, PPTS) was followed by desilylation (TBAF, THF) of the secondary one. Oxydation by PCC then afforded the ketone **4** (43% overall yield).

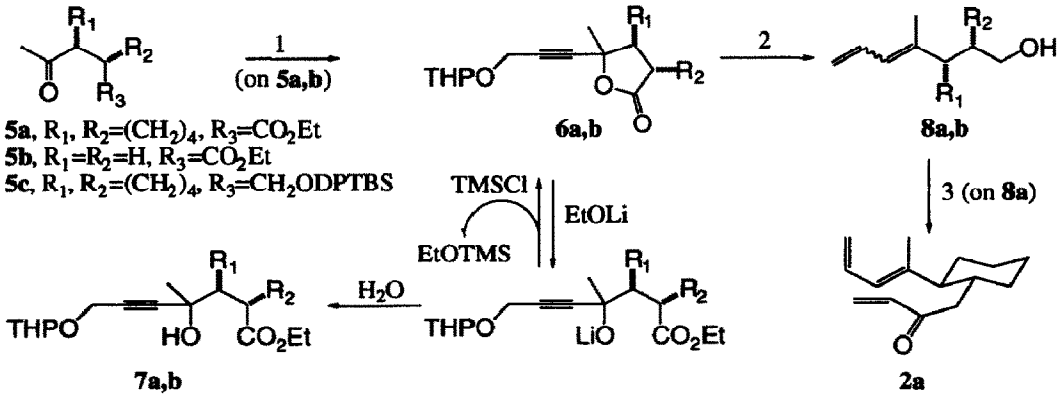
Attempted condensation of this ketone with various phosphorylated ylids or sulfur-stabilised carbanionic species, in order to generate the dienyl moiety proved unsuccessful.[2] The ketone was apparently devoid of reactivity for such nucleophilic additions. This could result either from steric hindrance, preventing approach of the reagent, or from rise of unfavourable steric interaction during the condensation, as it is tentatively represented. Should these hypotheses be accurate, the use of both a less sterically-demanding carbanionic

species and an acetylcyclohexane bearing another electrophilic center prone to intercept the developing alcoxide will allow the condensation to take place. These considerations led us to select a lithio acetylenic compound as nucleophilic reagent and to exercise a related ketoester, **5a**,[3] as model substrate.



1- *i*) CSA (0.1 eq.), MeOH, r.t., 1 day; *ii*) DPTBSCl (1 eq.), imidazole (2 eq.), DMF, r.t., 3 hours;
2- *i*) LAH (3 eq.), THF, r.t., 2 days; *ii*) $PhCH(OMe)_2$ (1eq.), PPTS (0.1 eq.), CH_2Cl_2, r.t., 1 day;
3- *i*) DHP (1.1 eq.), PPTS (0.13 eq.), CH_2Cl_2, r.t., 4 hours ; *ii*) TBAF (excess), THF, r.t., overnight; *iii*) PCC (1 eq.), AcONa (1 eq.), CH_2Cl_2, 10°C, 4 hours.

Addition of lithiated (*n*-BuLi, 1 eq., THF, 0°C) 3-tetrahydropyranyloxy-1-propyne (1.1 eq.) to a solution of cyclohexanecarboxylate **5a** in THF at -78°C resulted in the formation of a new product which proved to be lactone **6a**. TLC indicated also disappearance of the starting ester. However, removing the cooling bath and pouring the condensation mixture into brine resulted essentially in the isolation of hydroxester **7a**; only a reduced amount of compound **6a** was then present. Since **7a** was not clearly detected before the extraction process, it could be anticipated that the lactone, first formed, condensed with lithio ethoxide when temperature rised, hence giving the observed hydroxyester. Indeed, treating **5a** with the lithio reagent, then adding TMSCl to the resulting mixture in order to trap the released ethoxide, and stirring the mixture for 2 hours at room temperature resulted in the obtention of lactone **6a** as a mixture of two diastereomers in a fairly good yield (84%). Treatment of lactone **6a** with LAH[4] finally gave the diene **8a** (E/Z ratio= 7/3 (^{1}H NMR); unchanged in using a diastereomerically pure lactone). Ethyl levulinate itself -i.e. **5b**- was transformed into 4-methyl-4,6-heptadienol, **8b** (E/Z≈7/3), by using the same two-steps procedure.[5]



1- LiC≡C-CH_2O-THP (1.1 eq.), TMSCl (1.5 eq.), THF, -78°C-r.t., 20 hours; 2- LAH (3 eq.), THF, 45-50°C, 20 hours; 3- *i*) Tosyl chloride (1 eq.), DMAP (0.05 eq.) pyridine (5 eq.), 4°C, overnight; *ii*) KCN (1.8 eq.), DMSO, 85-90°C, 2 hours; *iii*) DIBAH (1 eq.), CH_2Cl_2, -78°C, 1 hour; *iv*) vinylmagnesium bromide (1 eq.), THF, r.t., 30 min; *v*) MnO_2 (excess), hexane, r.t., 1 day.

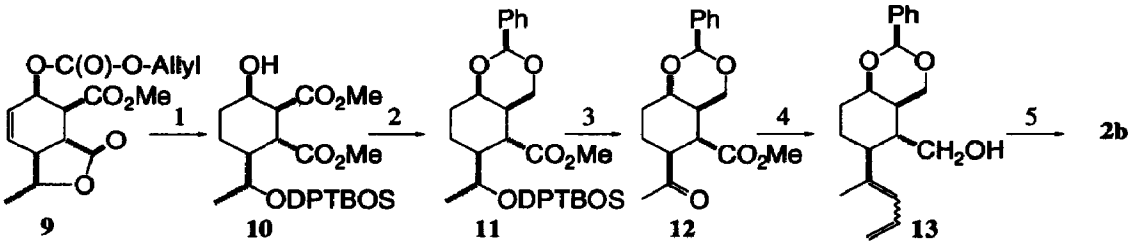
Submitting the protected ketoalcohol **5c** to the same condensation conditions did not proceed; most of the starting ketone remained unchanged. Thus it seems likely that the observed efficiency of the lactone formation

results essentially from trapping of the tetrahedral anionic intermediate by the adjacent ester group.

Final conversion of **8a** into trienone **2a** (Y=CO) was smoothly realized by using conventional reagents. Tosylation and treatment with KCN gave a nitrile in almost quantitative yield. Reduction with DIBAH in CH_2Cl_2 (90%), condensation with vinylmagnesium bromide in THF (84%), and finally oxidation with MnO_2 in hexane (88%) afforded the unsaturated ketone **2a**.

The use of the emerging methodology for preparing ketone **2b** (Y=CO) implied to transform the lactone moiety of **1** into a β-ketoester functionality and, at the same time, to protect selectively the existing α-ketoester group. After a few attempts, it appeared more convenient to start with the dehydrolactone **9**, an intermediate in the preparation of **1**. The hydroxyester which readily formed on methanolysis of **9**[1] was silylated with DPTBOSCl[6] in CH_2Cl_2 and in presence of both NEt_3 and 4-DMAP. Removal of the carbonate group under palladium catalysis[1] (98%), followed by hydrogenation (94%) then afforded the hydroxyester **10**. Treatment of **10** with $LiBH_4$ in THF gave selectively a diol (78%) which was condensed with α,α'-dimethoxytoluene in CH_2Cl_2. The resulting acetal **11** crystallised on standing (84%).

Removal of the protecting silyl group proved extraordinarily difficult whatever the conditions we used.[7] We succeeded finally in treating **11** with a mixture of TBAF (7eq.) and pyridinium fluorochromate (7 eq.) in CH_2Cl_2 (r.t., 6 d), what furnished directly the ketoester **12** (60%) as a white foam, besides unreacted **11** (34%).



1- *i*) CSA (0.1 eq.), MeOH, r.t., 2 days; *ii*) DPTBOSCl (1.1 eq.), NEt_3 (1.3 eq.), DMAP (0.1 eq.), CH_2Cl_2, r.t., 2 hours; *iii*) 2-ethylhexanoic (1.1 eq.), $Pd(Ph_3)_4$ (0.015 eq.), PPh_3 (0.11 eq.), CH_2Cl_2, r.t., 16 hours; *iv*) H_2 (1 atm.), 10% Pd/C, AcOEt; 2- *i*) $LiBH_4$ (1 eq.), THF, r.t., 2 hours; *ii*) α,α'-dimethoxytoluene (1.1 eq.), PPTS (0.05 eq.), CH_2Cl_2, r.t., 18 hours; 3- TBAF (7 eq.), pyridinium fluorochromate (7 eq.), CH_2Cl_2, r.t., 6 days; 4- *i*) $LiC{\equiv}CH_2OTHP$ (1.1 eq.), TMSCl (1.5 eq., THF, -78°C-r.t., 4 hours; *ii*) LAH (3 eq.), THF, 45-50°C, 1 day; 5- *i*) tosyl chloride (1 eq.), DMAP (0.05 eq.), pyridine (5 eq.), 4°C, overnight; *ii*) KCN (1.8 eq.), DMSO, 90°C, 2 hours; *iii*) DIBAH (1 eq.), CH_2Cl_2, -78°C, 1 hour; *iv*) vinylmagnesium bromide (1.2 eq.), THF, -78°C-r.t., 30 min; *v*) MnO_2 (20 eq.), hexane, r.t., 1 day.

Condensation of ketoester **12** with the lithium salt of the propargyl alcohol derivative as precedently proceeded well, giving the expected lactone as a mixture of two diastereomers (78%). Treatment with LAH then afforded diene **13** (65%; E/Z=7/2, by ^1H NMR).[8] Conversion of **13** into the target IMDA candidate, **2b** (68% overall), was performed without noticeable difficulty by using the same reactions as described above for the **8-2a** conversion. Subsidiarily, alcohol **13** was treated by acryloyl chloride (1.1 eq.) and triethylamine (1.2 eq.) in CH_2Cl_2 (0°C-r.t., 3 hours), what furnished acrylate **2c** (87%).

In conclusion, despite an ostensible simplicity, the intended **1-2b** conversion offered several difficulties, the foremost resulting from steric restriction of the acetyl centre in compound **4**. This was overcome in reducing the size of the attacking species and, more importantly, by coupling the condensation step with an intramolecular transesterification process. The stereoselectivity of the reduction step, leading to the dienes, was only modest (E/Z≈7/3). Nevertheless, since the pure *E* isomer could be isolated by chromatography, the overall process remains valuable in terms of simplicity and efficiency. The stereochemical outcome of IMDA reaction of these trienic compounds is reported in the following paper.

References and notes

1- Berthon, L.; Tahri, A.; Uguen, D. preceding letter.

2- The following conditions have been experimented: allyltriphenylphosphonium bromide/t-BuOK in THF or toluene; allyldiphenylphosphine oxide, allyl phenylsulfone, allyl phenylsulfide, 2-oxopropyl phenylsulfone, each being treated first by *n*-BuLi (*t*-BuOK with the latter) in THF, with or without added $CeCl_3$.

3- The ethyl ester of *anti*-2-acetylcyclohexanecarboxylic acid, **5a** (Bp 73°C at 0.1τ), was prepared (by Miss K. Beck, who is warmly acknowledged) by heating a solution of sulfolene (excess) and ethyl dehydrolevulinate (McMurry, J.E.; Blaszczak, L.C. *J. Org. Chem.* **1974**, *39*, 2217-2222) in chlorobenzene at 95°C for 2 days in a closed flask and hydrogenating (5% Pd/C, AcOEt) the resulting cycloadduct (93% overall yield).

4- Nayler, P.; Whiting, M.C. *J. Chem. Soc.* **1954**, 4006-4009. Surprisingly, LAH reduction of hydroxyester **7a** proceeded less satisfactorily.

5- a) *The condensation step*: a 1.3M solution of *n*-BuLi in hexane (7.8 ml; 10.1 mmol) was added to a solution of the propargylic derivative (11.1 mmol) in THF (20 ml) at -78°C. Stirring was pursued 15 mn at -78°C, then 1 hour at r.t.. The resulting solution was added dropwise *via* canula to a cooled (-78°C) solution of the ketoester (10.1 mmol) in THF (15 ml). The cooling bath was removed for 1 hour. The resulting pale yellow solution was brought again to -78°C, after that TMSCl (1.9 ml; 15.15 mmol) was added. The mixture was stirred for 1-2 hours then transferred, *via* canula, into a mixture of KOH (0.6 g), KH_2PO_4 (1.25 g), iced water (70 g), and ether (30 ml). After 1 hour, the aqueous layer was separated and extracted with ether (4x20 ml). The combined organic phases were washed with brine (2x20 ml), and dried ($MgSO_4$). Removal of solvents left an oil which was purified on silica gel (60H (Merck); 5% AcOEt/hexane). Starting from **5a**, the lactone **6a** was obtained as a pale yellow oil (2.45g, 83%), from which a pure diastereomer could be isolated by crystallisation from hexane (m.p. 60-61°C); ^{13}C NMR ($CDCl_3$, 50 MHz): 18.8 21.8, 22.3, 22.6, 23.6, 23.8, 25.1, 40.8, 45.7, 53.8, 61.8, 78.1, 80.7, 85.6, 96.7, 177.0; IR: 2220, 1775 cm^{-1}. The other diastereomer was an oil; ^{13}C NMR ($CDCl_3$, 50 MHz): 19.1, 21.4, 22.5, 23.0, 23.4, 26.0, 26.6, 30.3, 38.8, 43.7, 54.0, 62.1, 80.0, 83.5, 84.2, 96.7, 176.5; IR: 2220, 1775 cm^{-1}. b) *The reduction step*: LAH (1.37 g, 36 mmol) was dropped into THF (10 ml). The mixture was cooled to 0°C, afterwards a solution of the diastereomeric lactones (12 mmol) in THF (10 ml) was added dropwise. The resulting grey suspension was stirred for 20 hours at 45-50°C. After cooling, and dilution with ether (50 ml), aqueous saturated ammonium chloride (10 ml per gram of LAH) was added cautiously. The etheral solution was dried ($MgSO_4$). Evaporation was followed by flash-chromatography (60H (Merck) silica gel; hexane/AcOEt). Starting from **6a**, diene **8a** was obtained as an oil (1.8g, 83%); UV (EtOH): λ_{max}=238 nm (logε=4.2).

6- Gillard, J.W.; Fortin, R.; Morton, H.E.; Yoakim, C.; Quesnelle, A.; Daignault, S.; Guindon Y. *J. Org. Chem.* **1988**, *53*, 2602-2608. DPTBS derivatives could not be deprotected at a latter stage.

7- With TBAF, the only product was the corresponding lactone. Attempted ring opening of this lactone with lithium methoxide in THF did not prove useful, being only partial.

8- a) ***E*-13**: Rf 0.42 (9/9/2 hexane/CH_2Cl_2/AcOEt); ^1H NMR ($CDCl_3$, 200 MHz): 1.4-2.08 (m, 9H), 2.19-2.4 (m, 2H), 3.65 (d, 1H, *J*=11 Hz), 3.77 (dd, 1H, *J*=2.1 and 11 Hz), 3.9 (dd, 1H, *J*=2.3 and 12 Hz), 4.15 (m, 1H), 4.46 (d, 1H, *J*=12 Hz), 5 (dd, 1H, *J*=1.7 and 10.4 Hz), 5.17 (dd, 1H, *J*=1.7 and 16.8 Hz), 5.58 (s, 1H), 6 (d, 1H, *J*=10.5 Hz), 6.6 (td, 1H, *J*=10.5 and 16.8 Hz), 7.35-7.4 (m, 3H), 7.43-7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): 14.1, 29.8, 32.0, 35.7, 36.3, 48.6, 61.0, 69.0, 75.7, 102.3, 115.7, 126.3, 126.8, 127.0, 128.4, 129.0, 133.0, 139.0, 142.2; b) ***Z*-13**: Rf 0.53 (9/9/2 hexane/CH_2Cl_2/AcOEt); ^1H NMR ($CDCl_3$, 200 MHz): 1.4-1.8 (m, 7H), 1.82-2.2 (m, 2H), 2.25-2.68 (m, 1H), 2.8 (m, 1H (OH)), 3.55 (d, 1H, *J*=11 Hz), 3.7 (d, 1H, *J*=11 Hz), 3.9 (dd, 1H, *J*=2.3 and 12 Hz), 4.15 (d, 1H, *J*=2.5 Hz), 4.46 (d, 1H, *J*=12 Hz), 5 (d, 1H, *J*=10 Hz), 5.18 (d, 1H, *J*=16.7 Hz), 5.59 (s, 1H), 5.8 (d, 1H, *J*=9.9 Hz), 6.7 (td, 1H, *J*=10 and 16.7 Hz), 7.35-7.4 (m, 3H), 7.43-7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): 22.8, 25.8, 31.0, 35.9, 36.3, 48.6, 60.8, 69.0, 75.7, 102.3, 116.0, 126.3, 126.8, 127.0, 128.4, 132.2, 139.0, 142.0.

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