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A *C-B-A-D* Approach to Brassinosteroids; Generation of the *A-B-C* Ring System

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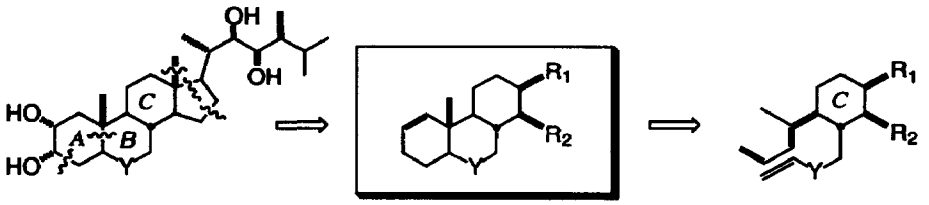
Abstract: *BF_3-catalysed intramolecular Diels-Alder cyclisation of ketone 2c has been shown to proceed, under kinetic conditions, through a chairlike* endo *transition state.*

Central in our approach to the total synthesis of the title compounds was the formation of the entire *A-B-C* ring system by intramolecular Diels-Alder (IMDA) reaction of a suitably substituted cyclohexane derivative featuring the *C*-ring.[2] Toward this end, trienyl compounds **1a** and **1b**, as well as the simpler model substrates **1c** and **1d** were prepared.[3] Success in the planned cyclisation should authorise a straightforward access to the *A-B-C* part of both castasterone and brassinolide; base-induced shift of the carbon carbon double bond to the $\Delta^{2,3}$ position being then followed by a face-selective bis-hydroxylation.[4] Results dealing with the outcome of IMDA reactions of compounds **1** are presented herein.



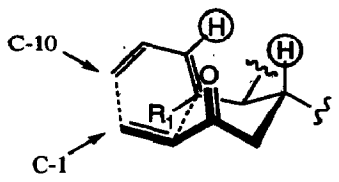
Castasterone, Y=CO
Brassinolide, Y=C(O)-O-

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

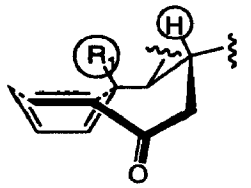
1a-d

Cyclisation of the vinylic ketones was first examined. IMDA reaction of related trienones, e.g. 1,7,9-decatriene-3-one, **3a**, and of the parent C-5 (and/or C-6) substituted derivatives has been studied extensively.[5-7] As a rule, the stereochemistry of the major bicyclic ketone formed under kinetic control is *cis*.[7e] This stereoselectivity is best accommodated in assuming that those cyclisations proceed through a boatlike transition state (TS) and various arguments have been presented to rationalise this rather astonishing inclination. Theoretical studies favour a synchronous two-steps mechanism with C-1/C-10 linkage the more developed in an early transition state;[6a,b] conformational preference of the hypothetical cyclodecenyl intermediate, as estimated from that displayed by cyclodecane, agrees effectively with the observed stereochemical outcome of the cyclisation process.[6c] The rise of an unfavourable interaction between the two circled hydrogen atoms in the chairlike TS, as shown below, has also been

alluded to;[7c] clearly, no such interaction appears in the boat conformation with trienones in which R_1 substituent is a hydrogen atom. Evaluation of emerging gauche interactions in each postulated TS led to similar conclusions.[5a]

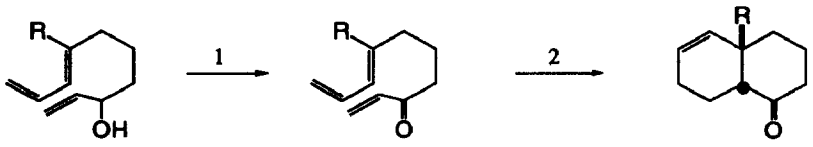


Chairlike Endo TS



Boatlike Endo TS

When R_1 designates a methyl substituent, as it is the case with ketone **1a** (or **1c**), it had to be expected that balance between the two postulated TS would not be so straightforward; a crucial point of our strategy.[8] Gauche interaction of the C-5/C-6 bond with either the C-7/C-8 or the C-7/methyl group one will develop in, respectively, the chairlike and the boatlike TS; the cyclisation should not be easy anyway. Indeed, whereas 1,7,9-decatriene-3-one, **4a**, cyclises spontaneously during oxidation of alcohol **3a** at room temperature to give **5a**,[7a] the 7-methyl analogue, **4b**, could be prepared efficiently by oxidation of alcohol **3b** in similar conditions (MnO_2, CH_2Cl_2, r.t., 2 days; 87%). Moreover, **4b** remained unchanged upon heating.



3a, R=H
3b, R=CH_3

4a,b

5a,b

1- MnO_2 (excess), CH_2Cl_2, r.t. (on **3a**: see ref.7a; on **3b**: present work); 2- **4a** only, under conditions 1

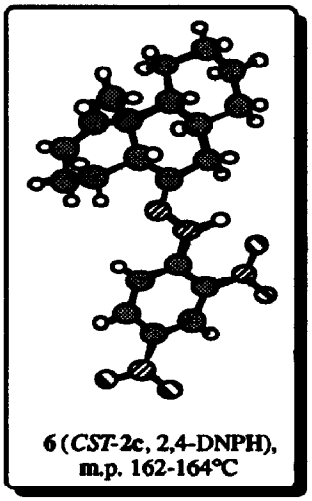
However, applying high pressure (10Kbar) to a solution of ketone **4b** in CH_2Cl_2 resulted in the formation of a new ketone (53%) whose structure was clearly established as **5b** by high-field NMR.[9] Interestingly, after several unfruitful experiments in using prevalent Lewis acids, it was found that the same ketone was also formed in treating a dilute solution of **4b** in CH_2Cl_2 by BF_3 etherate (0.6 eq.) at low temperature (-78°C) and neutralising the acid with NEt_3 (0.6 eq.) at the same temperature just before extraction.

These preliminary experiments did not provide precise information on the stereochemical feature -i.e. chairlike vs boatlike- of the transition state.[8] Nevertheless, the possibility to carry out the cyclisation of a 1,7,9-decatriene-3-one bearing a methyl substituent at position 7 was then ascertained and indeed, either applying high pressure or adding BF_3-Et_2O at -78°C to a dilute solution of **1c** in CH_2Cl_2 (the acid being neutralised before extraction as above) resulted in the isolation of a new ketone (54 and 35%, respectively), isomeric with the starting material (elemental analysis; ^{13}C NMR[10]). Both ^1H and ^{13}C NMR showed clearly the presence of a R_3C-CH=CH-CH_2 moiety. Precise structure determination proved puzzling however at this stage of the work. Fortunately, this ketone gave a 2,4-DNPH derivative, **6**, by treatment with 2,4-dinitrophenylhydrazine (1.1 eq.) under mild conditions (1:3 0.1N aqueous HCl/EtOH mixture; 5 hours, 30-35°C); recrystallisation from diisopropylether gave orange crystals (m.p. 162-164°C, 80%) suitable for X-rays analysis.

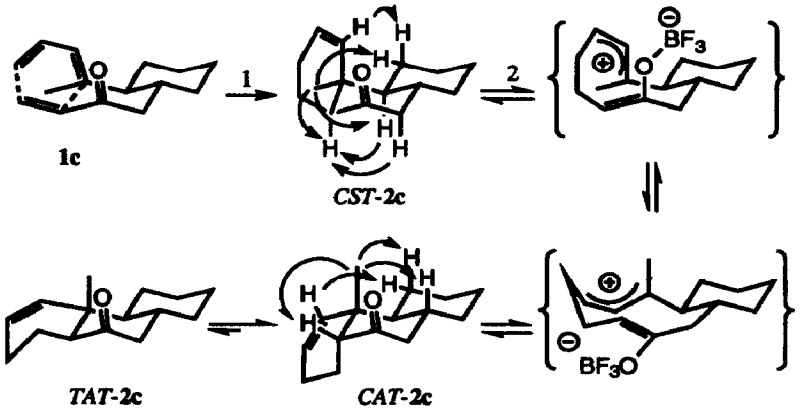
The projection of **6**, computer-generated from crystal data[11] showed clearly that the stereochemistry was *cis-syn-trans* (*CST*). Since the cyclised ketone proved stable in either slightly acidic or basic aqueous media, as verified independently, it could be concluded with some confidence that, *under kinetic conditions* (prolonged contact with BF_3

at -78°C failed to induce any isomerisation), IMDA reaction of ketone **1c** proceeded essentially through a chairlike *endo* transition state so as to give the *cis-syn-trans* cyclisation product, *CST*-**2c**. Subsequently, the *CST*-**2c** structure was unambiguously confirmed by further high-field NMR experiments.

Apparently, this result sounded the knell of our initial strategy. However, rising by c.a. 50°C the temperature of the BF_3-catalysed reaction mixture induced, to our delight, the isomerisation of the *CST* isomer into a new ketone to which *cis-anti-trans* -i.e. *CAT*-**2c**- structure was ascribed; *inter alia* on the basis of ROESY experiments.[12] Of course, the rather unusual mildness of the conditions in which this isomerisation occurred had to be accounted for. As shown below, we suggest tentatively that this rearrangement proceeds through a one-bond cleavage process; the *CAT*-**2c** isomer being presumably in equilibria with the less stable, not detected *trans-anti-trans* isomer (i.e. *TAT*-**2c**).



6 (*CST*-**2c**, 2,4-DNPH), m.p. 162-164°C



1- a) BF_3-Et_2O (0.6 eq.), CH_2Cl_2, -78°C, 3 hours; b) NEt_3 (0.6 eq.), -78°C;
2- a) same conditions as in 1a, then -30°C, overnight; b) 1b

Submitting a solution of **1a** in CH_2Cl_2 to high pressure conditions brought about the desired conversion albeit in low yield (23%). NMR data of the cyclised product agreed well with that displayed by **1c** and strongly suggested the *CST*-**2a** structure. As expected, use of Lewis-acids proved unsuitable; due to the presence of an acetal functionality, extensive degradation occurred. Finally, cyclisation of either acrylates **1b** and **1d** was attempted. Whatever the conditions we used -e.g. heating or applying high pressure-, these esters failed to give any cyclised product. Use of BF_3-Et_2O as above induced only decomposition of the starting material. Improper combination of dipole moments or unfavourable distortion in the ester functionality, as argued in related cases,[13] could provide a rational for the observed lack of reactivity.

In conclusion, the experiments presented herein established unambiguously both the feasibility and the stereochemical outcome of the intended IMDA reaction: cyclisation of ketone **1c** passes through an *endo* chairlike transition state; formation of the observed kinetic product -i.e. *CST*-**2c**- can occur exclusively *via* this spatial arrangement of the starting ketone. Hence, these results seem confirming that dichotomy in energy level of the two possible -i.e. boat vs chair- *endo* TS results essentially from the adventitious development of unfavourable non-bonded interactions in the C-5/C-7 area of the decatrienone system.[5a] With decatrienones bearing a hydrogen atom at C-7, extra unfavourable interactions appear in the chairlike conformation: the "boat" product predominates.[5a] But when similar interactions are developed in either the boatlike or the chairlike ordering as it is the case with C-7-substituted decatrienones, then the chair is preferred.[7e]

With regard to our synthetic purpose, a practical conclusion is that generation of the *D*-ring from *CST*-**2a** should be performed before adjusting the stereochemistry of the *A-B* ring junction. Results along this line will be reported in due course.

References and notes

1- To whom any requests concerning the crystallographic analysis should be addressed.

2- For other IMDA approaches to synthesis of steroids, see: Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3-16; Marinier, A.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 6215-6218; Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J. *J. Am. Chem. Soc.* **1988**, *110*, 2674-2676; Stork, G; Sherman, D.H. *J. Am. Chem. Soc.* **1982**, *104*, 3758-3759.

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8- Unlike with ketone **3b**, the boatlike *endo* TS for cyclisation of **1a** (or **1c**) should lead theoretically to a cyclised product diastereomeric with that formed through the corresponding chairlike *endo* TS.

9- We warmly thank Dr. G. Jenner for having performed the high pressure experiments. These thanks have to be extended to Drs R. Graaff and J. Raya for achievement of the high-field NMR (COSY, ROESY) experiments and to Dr. J.-M. Trendel for helpful assistance in treatment of NMR data.

10- Selected ^{13}C NMR data ($CDCl_3$, 50MHz): *i)* **5b**: 21.5, 22.0, 22.3, 28.9, 36.9, 38.5, 40.4, 54.6, 126.8, 135.3, 213.3; *ii)* *CST*-**2c**: 18.7, 22.0, 25.4, 26.0, 26.7, 27.8, 35.1, 37.4, 41.3, 49.5, 50.7, 50.9, 128.6, 129.7, 210.7; *iii)* *CAT*-**2c**: 20.7, 24.6, 25.2, 26.8 27.5, 30.9, 31.6, 31.9, 39.4, 40.6, 45.1, 56.3, 125.0, 135.6, 216.9.

11- Crystal data for **6** ($C_{21}H_{26}N_4O_4$; M=398.5): monoclinic, space group $P2_1/c$, a=17.050(7), b=13.740(5), c=8.637(3) Å, β=100.11(2)°, V=1991.9 $Å^3$, z=4, dcalc=1.947 gcm^{-3}, μ(CuKα)=7.270 cm^{-1}, λ=1.5418 Å. Intensities of 2433 independent reflections with θ in the range 3-51° were measured on a Philips PW1100/16 diffractometer at -100°C achieved in using a local build gas flow device, θ/2θ flying step-scan mode, dimensions of the crystal 0.35x0.16x0.15 mm. The structure was solved by direct methods and refined by full-matrix least squares first with isotropic and then with anisotropic thermal parameters for all non hydrogen atoms using 1610 observed reflections with $I>3\sigma(I)$. Empirical absorption corrections (abs min and max=0.57/1.12). The hydrogen atoms were located in difference Fourier maps and included in structure factor calculation but not refined. Final R and Rw values are 0.042 and 0.061, GOF=1.108 for p+0.08 in $\sigma^2(Fo)=\sigma^2_{count} + (pI)^2$. Tables of atomic coordinates, a list of bond distances and angles, a list of thermal parameters and a list of observed and calculated structure factors have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (U.K.). They may be obtained on request from the Director by citing the full reference to this communication.

12- ^1H NMR clearly showed that the observed isomerisation of *CST*-**2c** did not result from migration of the carbon carbon double bond. Since epimerisation of the starting ketone into the *TST* isomer is unlikely, the NOE occurring between the angular α-keto hydrogen atom and those of the methyl group is strongly indicative of the *CAT*-**2c** structure of the rearranged ketone.

13- a) Jung, M.E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469-5470; b) Boeckman, R.K.; Demko, D.M. *J. Org. Chem.* **1982**, *47*, 1789-1792.

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