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

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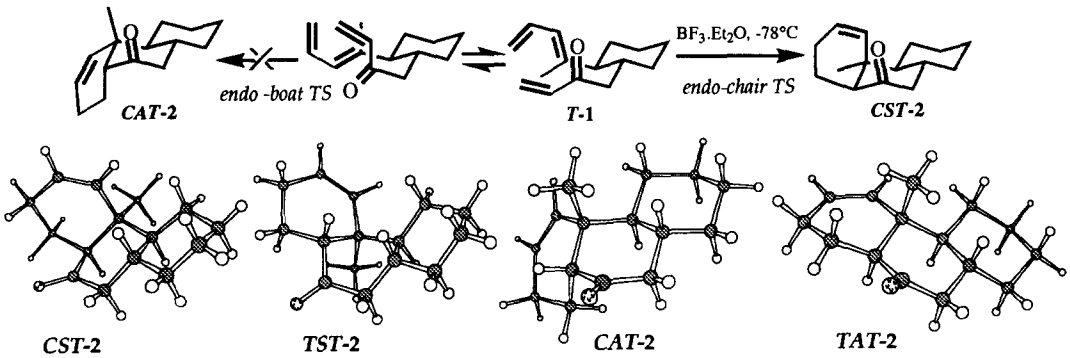
Abstract: *Thermal intramolecular Diels-Alder cyclisation of the ketone* **C-1** *proceeds through an* exo *transition state to give the ketone* **CAT-2**. © 1997 Published by Elsevier Science Ltd.

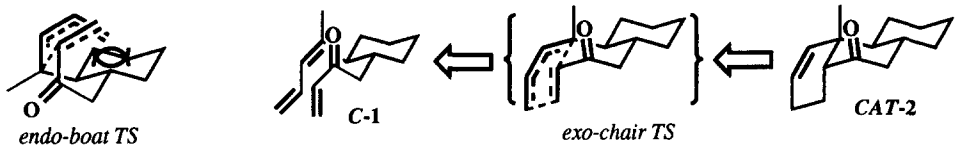
Previously, we reported that low temperature (ca -78 °C), BF_3-catalysed, intramolecular Diels-Alder (*i.e.* IMDA) cyclisation of the *trans* ketone ***T*-1** proceeded, under kinetic control, through an endo-chair transition state to give a tricyclic ketone whose the structure was unambiguously established as being ***cis-syn-trans*-2** (***CST*-2**) by *inter alia* X-ray analysis of the corresponding 2,4-dinitrophenylhydrazone (*i.e.* DNPH).[1]



Another result of that study was the observation of an isomerisation of the kinetic product ***CST*-2** into a structurally-related hydrophenanthrenone when the temperature of the cyclisation medium rose to -30 °C. NMR of this new product indicated clearly that the carbon-carbon double bond was retained at the Δ^1 (steroid numerotation) position. Furthermore, a NOESY experiment revealed a significative interaction between the angular methyl group and a proton resonating at δ=1.95 ppm (200 MHz), which we considered then (erroneously, as shown below) as being located at the A-B ring junction, close to the carbonyl group as in ***CST*-2**. Given these NMR data, both the ***TST*-2** structure, which would result from epimerisation of ***CST*-2** at C-5, and the ***TAT*-2** structure were excluded. Additionally, an energy calculation indicated that the ketone ***TST*-2**, in which the central ring has to be necessarily in a boat conformation, should be disfavoured over the *cis* isomer ***CST*-2** by 3.7 Kcal/mol.[2] Accordingly, structure ***CAT*-2** was tentatively assigned to that rearrangement product of ***CST*-2**.

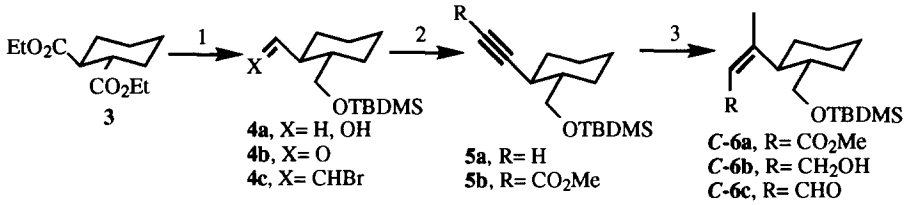
A regrettable consequence of this result was that our planned synthesis of brassinosteroids by a strategy based on the use of such an IMDA process could be hardly completed by starting from the trienone ***T*-1**. In order to validate our initial plan however and, additionally, to establish more firmly the structure of that isomerisation product of ***CST*-2**, we decided to prepare, then to test under IMDA conditions, the *cis* isomer of ***T*-1**, ***C*-1**.

As depicted here, due to stringent steric interactions in hypothetical *endo* transition state, concerted cyclisation of ***C*-1** should occur exclusively through an *exo* TS, to give the ketone ***CAT*-2**. This proved to be the case.

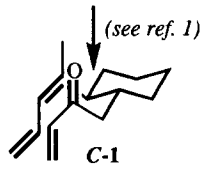


The scheme we used previously to obtain the *trans* diene ***T*-1** gave a 7/3 mixture of ***T*-1** and ***C*-1**, respectively. Unfortunately, despite repeated, laborious, chromatographies on silica gel, it proved impossible to isolate the pure ketone ***C*-1** from that mixture and, accordingly, a different approach, based, as shown below, on the stereoselective methylcupration of a 3-substituted propiolic ester, was explored.

LAH reduction of the diester **3**[3] gave a diol, the corresponding mono-sodium salt of which was treated with TBDMSCl in THF to give **4a**.[4] Swern oxidation of **4a** furnished the aldehyde **4b**, which was condensed with bromomethyl triphenylphosphorane. The resulting bromo derivatives ***E*-4c** and ***Z*-4c** (*E*/*Z* ratio not determined) were reacted with BuLi in THF to provide the acetylenic compound **5a**. Subsequent treatment of **5a** by butyllithium in THF, then by methyl chloroformate gave the desired propiolic derivative **5b**.



Reagents and Conditions: 1- *i*) LAH (1.6 eq.), ether; r.t. to reflux, 12 hours (85%); *ii*) NaH (1 eq.), THF; r.t., 0.5 hour , then TBDMSCl (1 eq.), TBAI (0.1 eq.); -15° to r.t., 12 hours (90%); *iii*) DMSO (1.7 eq.), $(COCl)_2$ (1.5 eq.), TEA (4 eq.), THF; -78°C to r.t., 0.5 hour (97%); *iv*) $BrCH_2PPh_3Br$ (1.1eq.), t-BuOK (1 eq.), THF; -78°C to r.t., 1 day (33%); 2- *i*) BuLi (2 eq.), hexane/THF; °C, -78°C, 1 hour, then r.t., 1 hour (33%); *ii*) BuLi (1 eq.), THF; -78°C, 0.5 hour, then $ClCO_2Me$ (1.1 eq.); -78°C to r.t., 1 hours (95%); 3- Me_2CuLi (2.5 eq.), ether/THF; -78°C, 30 hours, then MeOH (96%); 4- *i*) DIBA-H (2.2 eq.), CH_2Cl_2; -78°C, 1.5 hour (91%); *ii*) $BaMnO_4$ (10 eq.), CH_2Cl_2; r.t., 16 hours (97%); CH_3PPh_3I (2 eq.), BuLi (1.8 eq.), THF; -78°C, 1 hour, then r.t., 0.5 hour (95%).



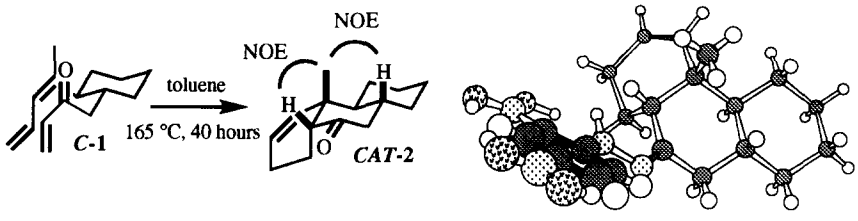
The carbocupration step was performed very efficiently by treating the ester **5b** with lithium dimethylcuprate in THF at -78 °C, for 30 hrs , which furnished the pure *cis* ester ***C*-6a** (NMR, NOE) in excellent yield (96 %).[5] DIBAH reduction of ***C*-6a** and oxidation of the resulting alcohol ***C*-6b** with $BaMnO_4$ led to the *cis* aldehyde ***C*-6c**, which was condensed with methylene triphenylphosphorane to afford the diene ***C*-6d**. Finally, elaboration of the diene ***C*-6d** to the pure (NMR) enone ***C*-1** (14 % overall) was completed as described for the ***T*-6d-*T*-1** conversion.[1]

Attempted BF_3-catalysed cyclisation of the trienone ***C*-1** under various temperature conditions (ca -78 °C to room temperature) proved disappointing, the only observed reaction being the full decomposition of the starting material as soon as the temperature reached -40 °C. By contrast, heating a 0.1 M toluene solution of ***C*-1** at 165 °C, in a sealed glass tube previously washed with pyridine, resulted in the clean formation of a *single* ketone (81 %),

isomeric (^1H, ^{13}C NMR) to both ***CST*-2** and its rearrangement product (*vide supra*), and to which structure ***CAT*-2** could be safely ascribed as follows.

On the one hand, high field NMR experiments (NOESY, TOCSY, HMQC, HBMC), performed on a benzene-d_6 solution of that new ketone, revealed *inter alia* the indicated correlations, consonant with the ***CAT*-2** structure.[6] On the other hand, treatment of that ketone with 2,4-dinitrophenylhydrazine furnished a reddish solid. Though that derivative appeared homogenous in TLC under various elution conditions, it was, in fact, a mixture of two isomers (NMR).[7] Examination of that compound with a microscope revealed that it was indeed a mixture of orange prisms and clustered salmon needles which could be fractionated mechanically with tweezers under a hand magnifying glass. The efficiency of this separation process was ascertained by ^{13}C NMR of each individual DNPH. Recristallisation of the orange DNPH in a nitromethane/water mixture resulted in the formation of a single crystal (m.p. 185-186 °C), which proved suitable for X-ray analysis.

The structure shown, generated from crystal data,[8] reveals clearly the *CAT* ordering of the tricyclic system. We have been unable so far to obtain useful crystals of the second DNPH. However, NMR data at hand strongly suggest that it is isomeric with the ***CAT*-2** DNPH at the carbon-nitrogen double bond. Notwithstanding this subsisting structural uncertainty, it is doubtless however, given the whole set of collected analytical informations, that the thermal IMDA product of ***C*-1** is the ketone ***CAT*-2**.



***CAT*-2** DNPH m.p. 185-186 °C

In conclusion, the structure of the product obtained by isomerisation of ***CST*-2** (*vide supra*) is not the ***CAT*-2** isomer and both our earlier structural assignement and the mechanism of isomerisation then proposed have to be corrected. That error resulted possibly from an inaccurate consideration of the calculated energy of each ketone **2**. We assumed that an equilibrium between ***CST*-2** and its isomerisation product was reached, in which case the ***TST*-2** structure had to be ruled out since the calculated energy gap (ca 3.7 Kcal) for the ***CST*-2/*TST*-2** couple does not fit the observed 2/1 ratio. Supposing that, due to the conditions in which that rearrangement took place (microscale experiment, sample withdrawal via syringe), moisture was adventitiously introduced into the cyclisation mixture, then a Δ^5-enol boronate of ***CST*-2** could have formed and its subsequent kinetic protonation, which should occur on the less hindered β-face, would have given preferentially the thermodynamically-disfavoured ***TST*-2** isomer, which we consider now as being the actual isomerisation product of ***CST*-2**. In that event, our wrong interpretation of the NOE effect between the methyl substituent and the proton appearing at δ 1.95 ppm in the ^1H NMR spectra of that rearranged product can be understood by noting that the hydrogen atom attached at C-10 of ***TST*-2** lies, in the minimised structure of that ketone, inside the deshielding cone of the carbonyl group and should, accordingly, resonate at an anormaly high field. Experiments aimed at proving these assertions are now in progress.

More importantly, thermal cyclisation of the *cis* diene ***C*-1** has been shown to give the tricyclic ketone ***CST*-2** Since epimerisation at C-5 in that tricyclic ketone should be achieved without major difficulties, this result paves the way for an access to brassinosteroids by an IMDA strategy. Results along this line will be disclosed in due course.

Acknowledgements: Thanks are due to the Région Alsace and to the CNRS for a grant (to T. Z.).

References and Notes

1- Tahri, A.; Uguen, D.; De Cian, A.; Fischer, J. *Tetrahedron Lett.*, **1994**, *35*, 3945-3948.

2- The 3D structures of ketone **2** have been obtained by using the energy-minimisation package of the Chem-3D® software.

3- The diester **3** was prepared in good yield (85 %, overall) by heating at 90±2 °C a 0.6 M toluene solution of diethyl fumarate and added sulfolene (1.2 eq.) for 5 days, followed by hydrogenation (H_2 (1 bar), 5% Pd/C, AcOEt; r.t.) of the resulting *trans* diethyl cyclohexene-3,4-bis-carboxylate ($Bp_{0.1}$ 84 °C).

4- McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388-3390.

5- CuI (9.2 g, 2.5 eq.) was placed in a 500 ml flask. After usual flame-drying and thorough deaeration operations, freshly-distilled THF (100 ml) was added with a syringe. The resulting suspension was cooled to 0 °C and a 1.6 M ethereal solution of MeLi (58.7 ml, 4.8 eq.) was slowly added. The initial brownish-yellow colour faded progressively. After 15 mn of stirring at 0 °C, the pale-yellow solution was cooled to -78 °C, with formation a white precipitate. Addition of a solution of the ester **5b** (6 g; 19.3 mmol) in THF (60 ml) to that suspension, at such a rate that the *inside* temperature was maintained at -78 °C, resulted in the formation of a lemon solution, which was stirred at that temperature for 30 hrs. A flask containing well-deaerated, dried, methanol (500 ml) was placed in the same cooling bath, and, as soon as the temperature of the methanol reached -78 °C, the carbocupration mixture was transferred as rapidly as possible (ca 30 s), by a canula, into the alcohol, the content of both flasks *being imperatively kept at -78 °C throughout*; rise of the temperature resulted in partial isomerisation of ***c*-6a** to the corresponding *E* ester. After 15 mn of stirring at -78 °C, the resulting mixture was brought to room temperature and diluted with ether (150 ml), then with 10 % aqueous ammonium chloride (200 ml) and 15 % ammonia (50 ml). An usual extraction process (ether), followed by washing with 10 % NH_4Cl and brine, drying ($MgSO_4$), evaporation of the solvents, and filtration on silica gel gave the ester ***c*-6a** as a colourless oil (6.05 g; 96 %). Selected data: *i*) **5b**: $Bp_{0.05}$ 122-123 °C; C, H (%): 65.8, 9.74 (calc.: 65.76, 9.51) ^{13}C NMR (50 MHz): 5.61, 5.67, 18.2, 25.18, 25.28, 25.81, 28.48, 30.62, 31.62, 43.73, 52.29, 65.4, 73.56, 92.18, 154.2; ***C*-1**: C, H (%): 73.33, 11.55 (calc.: 73.4, 11.63); ^1H NMR (200 MHz): -0.01 (s, 3H), 0 (s, 3H), 0.87 (s, 9H), 1.06-1.88 (m, 8H), 1.7 (s, 3H), 1.9-1.99 (m, 1H), 2.48 (td, J= 4.3, 10.8 Hz, 1H), 3.2 (dd, J=3.4, 9.9 Hz, 1H), 4.92 (dd, J=2.1, 10.2 Hz, 1H), 5.06 (dd, J=2.2, 16.75 Hz, 1H), 5.85 (d, J=10.9 Hz, 1H), 6.66 (td, J=10.5, 16.8 Hz); ^{13}C NMR (50 MHz): 5.37, 5.43, 18.37, 19.49, 26.01, 26.11, 26.43, 29.71, 31.2, 41.41, 41.47, 66.1, 114.39, 127.32, 132.95, 142.14. The NMR spectra have been recorded in $CDCl_3$.

6- ***CAT*-2**: ^1H NMR (600 MHz, C_6D_6): 0.75-1.2 (m, 4H; C(12)H_2, C(13)H_2), 0.85 (s, 3H; CH_3), 1.2-1.45 (m, 2H; C(8)*H*, C(9)*H*), 1.25-1.9 (m, 8H; C(3)H_2, C(4)H_2, C(11)H_2, C(14)H_2), 1.98 (t, J=14 Hz, 1H; C(7)*Ha*Hb), 2.2 (dd, J= 3, 14 Hz, 1H; C(7)Ha*Hb*), 2.3 (d, J=12 Hz, 1H; C(5)*H*, 5.52 (m, 2H; C(1)*H*, C(2)*H*); ^{13}C NMR (150 Mz, C_6D_6): 22 (CH_3), 24 (C4), 25.5 (C12), 27 (C3, C13), 27.5 (C11), 35.5 (C14), 38 (C8), 40.5 (C10), 46.5 (C7), 47 (C9), 59 (C5), 125.5 (C2), 136 (C1), 216 (C6).

7- ***CAT*-2** DNPH: *i*) orange prisms: m.p. 185-186 °C; ^{13}C NMR (50 MHz, $CDCl_3$): 21.94, 22.39, 25.22, 25.87, 26.12, 26.73, 34.63, 37.73, 39.3, 39.89, 44.85, 47.16, 116.23, 123.67, 125.05, 128.93, 130, 135.6, 137.5, 145.34 *ii*) salmon needles: ^{13}C NMR (50 MHz, $CDCl_3$): 21.7, 24.9, 25.4, 26.1, 26.2, 31.5, 35, 36.9, 39.1, 47.2, 52.3, 116.4, 123.6, 125.2, 128.8, 129.9, 135.7, 145.3, 164.

8- a) Crystal data for ***CAT*-2** DNPH (m.p. 185-186 °C): $C_{21}H_{26}N_4O_4$, M.W.= 398.47, monoclinic, space group C2/c, a= 27.209(3), b= 8.4672(6), c= 20.700(1) Å , β= 121.513(6) °, U= 4065(1) $Å^3$, Z= 8, dcalc= 1.30 gcm^{-3}, μ (MoKα)= 0.086 mm^{-1}. Data were collected at room temperature using graphite monochromated MoKα radiation (λ= 0.7107 Å) on a Nonius-CAD4-F diffractometer and a crystal of dimensions 0.40*0.30*0.20 mm^3. 4403 reflections were collected (2.5 °< θ < 26.28 °). 1696 were unique and with I>3σ(I). Nor decay nor absorption corrections were applied. The structure was solved using direct methods and refined against |F| (full matrix, $\sigma^2(F^2) = \sigma^2_{counts} + 0.0064\ F^4$). Hydrogen atoms were introduced as fixed contributors (C-H= 0.95 Å, B(H)=1.3*Beqv of attached C). Final results : R(F)= 0.042, Rw(F)= 0.062, GOF= 1.171, largest residues in final difference map= +0.86/-0.42 $eÅ^{-3}$. For all computations the Nonius OpenMolen Package[8b] on a DEC Alpha 3600S computer was used; b) Fair, C.K. in MolEN. An Interactive Intelligent System for Crystal Structure Analysis. Enraf-Nonius, Delft, The Netherlands, 1990.

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