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Generation of the *Trans-Anti-Trans* A-B-C Ring System of Castasterone by Intramolecular Diels-Alder Reaction

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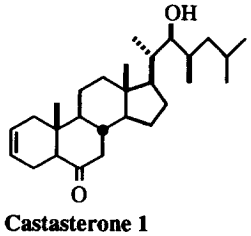
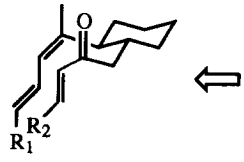
Abstract: By heating at 165 °C, the cyclohexane derivative **2d** afforded the tricyclic ketone **3d**, which, by sequential oxidation, hydrogenation, epimerisation, and basic treatment, furnished the cyclopropyl ketone **10**, a masked form of the target ketone ***TAT*-4**.

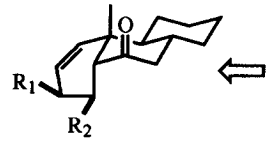
As part of a continuing effort to generate the A-B-C ring system of castasterone **1** by an intramolecular Diels-Alder (IMDA) reaction, we showed previously that the cyclohexane derivative **2a**, used as a model substrate, cyclised efficiently in thermal conditions to afford the hydrophenanthrenone **3a**.[1]



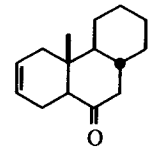
Castasterone 1



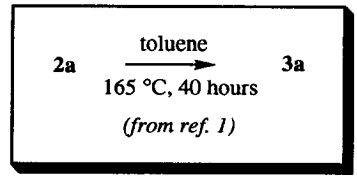
2a, R_1=R_2=H
2b, R_1=H; R_2=SO_2Ph
2c, R_1=H; R_2=CO_2Me
2d, R_1=SPh; R_2=H
2e, R_1=SPh; R_2=Tosyl

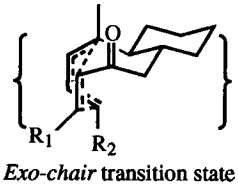


3a-e



***TAT*-4**





Exo-chair transition state

As can be seen, a relatively-high temperature (ca 165 °C) was required to observe the cyclisation of **2a** into **3a**, which was explained by assuming that this IMDA process occurs via the indicated *exo-chair* transition state.

Pursuing this preliminary study, we next examined the IMDA reaction of the related cyclohexane derivatives **2b-e** with the hope that presence of either an additional electron-withdrawing group (Tosyl, CO_2Me) or an electron-donor substituent (PhS) at the termini of, respectively, the ketovinyl and the butadiene residue of **2a** would facilitate this IMDA process and thus permit to operate at lower temperature. Subsidiarily, the phenylthio substituent should make feasible the required **3** to **4** conversion; for instance, hydrogenolysis, with allylic transposition, of the carbon-sulfur bond in the IMDA product **3d** would deliver the *cis-anti-trans* isomer (*i.e.* ***CAT*-4**) of ketone **4**, which, theoretically, should epimerise at C-5 (steroid numbering) to afford the desired *trans-anti-trans* isomer ***TAT*-4**. Though another means proved necessary to carry out this final transformation, we are pleased to report herein that implementation of a sulfur-centered substituent in **2a** made possible the planned **2**- to **4** conversion.

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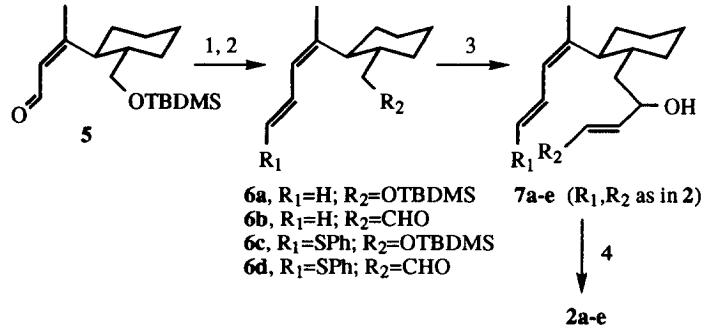
The substrates **2a** and **2b** were prepared as previously described by first condensing the aldehyde **5** with methylene triphenylphosphorane to form the dienyl derivative **6a**, which was then converted into the aldehyde **6b** by means of classical methodology. Ensuing condensation of **6b** with either vinylmagnesium chloride[1] or *E*-β-iodovinyl *p*-tolylsulfone[2] furnished the allylic alcohols **7a** and **7b**, which were reacted with the IBX reagent[3] to give **2a** and **2b**, respectively, Optionally, condensation of the aldehyde **6b** with methyl *E*-β-iodoacrylate in presence of $CrCl_2$-$NiCl_2$ in THF gave the alcohol **7c**, which was similarly oxidised into **2c**.

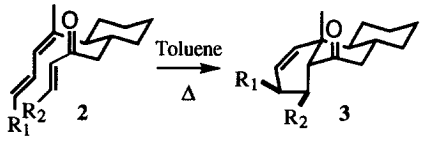
1- for **6a**: see ref. 1; for **6c**: diethyl phenylthiomethylphosphonate (2 eq.), 1.6M (in hexane) *n*-BuLi (1.8 eq.), THF (11 ml/mmol); - 78 °C to room t., 1.5 hours (87%); 2- **6c-6d** conversion: same conditions as for the **6a-6b** conversion (see ref. 1); 3- for **7a** and **7d**, see ref 1; for **7b** and **7e**, see ref. 2; for **7c** (R_2=CO_2Me): methyl β-iodoacrylate (1.3 eq.), $CrCl_2$ (4 eq.), $NiCl_2$ (0.01 eq.), THF (3 ml/mmol); room t., 1 hour (73%); 4- IBX (1.8 eq.), DMSO (3 ml/mmol); room t., 1 hour (see ref.3).



In a like manner, condensation of the aldehyde **5** with diethyl phenylthiomethylphosphonate afforded the phenylthiobutadiene derivative **6c**, admixed with its *Z,Z* isomer ***Z,Z*-6c** (**6c**/***Z,Z*-6c**=3/1, by NMR). At this stage, it was possible to fractionate this mixture by chromatography, the pure *Z,E* isomer **6c** being then transformed into compounds **2d** and **2e** by the sequences used precedently for the **5**-**2a** and the **5**-**2b** conversion, respectively. Later, however, it proved unnecessary to perform this separation (*vide infra*) and the preceding **6c**/***Z,Z*-6c** mixture was similarly converted into mixtures of either **2d** or **2e** with their respective *Z,Z* isomer (same isomeric ratio).

The thermal behaviour of compounds **2b-d** was then examined by heating at various temperatures, in a sealed tube and under an argon atmosphere, diluted toluene solutions of each substrate (Table).

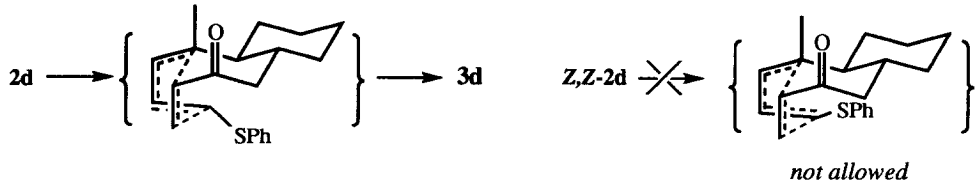
Table:



Substrat	Conditions			Products, Yield[a]
	$[2]_0 \times 10^2$ (mol/l)	T (°C)	t (days)	
2a (R_1=R_2=H)	9	165	2	**3a**, 81%[b]
2b (R_1=H; R_2=Tosyl)	5	100	1	**3b**, 86%
2c (R_1=H, R_2=CO_2Me)	2	110	2.5	**3c**, 86%
2d (R_1=SPh, R_2=H)	3	165	4	**3d**, 90%[c]
2e (R_1=SPh, R_2=Tosyl)	3	95	2	**3e**, 24%[d]

a- Isolated Yields.
b- From ref.1
c- From a 3/1 mixture of, respectively, **2d** and its *Z,Z* isomer (i.e.***Z,Z*-2d**) was isolated the sulfide **3d** (68%) besides unreacted ***Z,Z*-2d** (21%).
d- Partially decomposed (NMR) starting material was also isolated.

In each case, an unique IMDA product with structure **3** was formed as established unambiguously by NMR.[4] It follows that, irrespective of the substitution pattern, the thermal cyclisation of *trans*-1,2-disubstituted cyclohexane derivatives **2**, in which the configuration of the 1,1-disubstituted butadiene unit is *Z*,[5] proceeds exclusively by an *exo-chair* transition state.[6] The reluctance of ***Z,Z*-2d** to cyclise in conditions where its *E,Z* isomer **2d** gives **3d** validates in some way this mechanistic hypothesis: as shown, should an *exo-chair* transition state be the actual intermediate, such a spatial arrangement will be precluded in the former case due to a severe steric interaction of the phenylthio substituent with the cyclohexane residue.



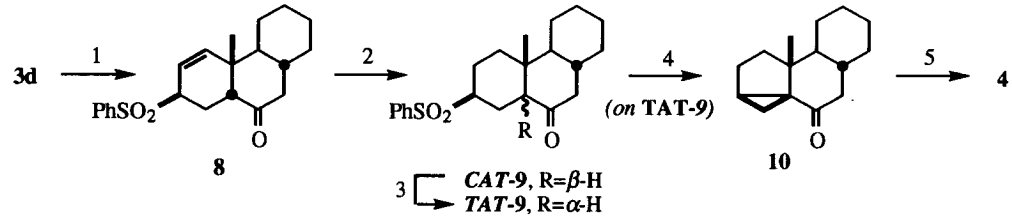
not allowed

Though moderate, the effect of the selected electron-withdrawing substituents on the rate of these IMDA reactions was perceptible: appendage of either a tosyl or a methoxycarbonyl group to the electrophilic carbon-carbon double bond facilitates the cyclisation process (Compare entries 1 and 2 (or 3)). By contrast, adjunction of a phenylthio substituent to the dienyl residue of **2a** was either without significant effect (Compare entries 1 and 4) or detrimental (Entry 5), the cyclisation reaction being then accompanied, for unclear reasons, by decomposition of the starting material, especially at higher temperature.

Conversion of the IMDA product **3d** into the ketone **4** was next studied.

Attempted hydrogenolysis of **3d** by treatment with lithium in ammonia (or ethylamine) proved not really useful, leading to complex, untractable, mixtures. Equally unrewarding was the reaction of the corresponding sulfone **8**, prepared by oxidising the sulfide **3b** with H_2O_2 in presence of ammonium molybdate, with various reducing reagents (NaHg/MeOH, $LiBEt_3$-$PdCl_2$.DPPA, etc...).

A more satisfactory result was obtained by first hydrogenating **8** to form the saturated keto sulfone ***CAT*-9**. By treatment with *p*-toluenesulfonic acid (PTSA) in refluxing chloroform, ***CAT*-9** epimerised smoothly into its *trans-anti-trans* isomer ***TAT*-9**, which crystallised out during the reaction. Hence, this equilibrium could be completely shifted toward the desired ***TAT*-9** isomer, eventually isolated in good yield by a simple filtration.



Reagents and conditions: 1: 30% H_2O_2 (3 eq.), ammonium molybdate (0.1 eq.), MeOH (3ml/mmol); 0 °C to room t., 40 min (81%); 2- H_2, 5% Pd/C, AcOEt; room t., 1 day (90%); 3- PTSA (0.3 eq.), $CHCl_3$; reflux, 1 day (83%); 4- *t*-BuOK (5.4 eq.), *t*-BuOH (22 eq.), DMF (10 ml/mmol); 80 °C, 2 hours (84%); 5- PTSA (0.1 eq.), LiBr (1 eq.), DMF; 135 °C, 5 hours (56%).

As could be anticipated from relevant literature,[7] the keto sulfone ***TAT*-9** cyclised smoothly in basic conditions (excess *t*-BuOK, DMF) to afford the cyclopropylketone **10**, which then isomerised into the target unsaturated ketone **4** by treatment with APTS and LiBr as recommended in a strongly related case.[8]

In summary, as observed previously with the simpler term **2a**, the IMDA reaction of compounds **2b-e** affords exclusively cyclised products having the *cis-anti-trans* stereochemistry, presumably via an *exo-chair* transition

state. Increase of the dienophilicity of the vinylketone moiety of **2a** by its substitution with additional electron-withdrawing groups allowed lower temperatures, the isolated yield in cyclised product being not substantially improved however. Attachment of a phenylthio group to the butadiene residue of **2a** proved much rewarding. In the event, though the rate of the IMDA reaction was not affected, as compared to the simpler substrate **2a**, the allylic sulfide **2d** which then formed could be efficiently transformed into the desired hydrophenanthrenone derivative ***TAT*-4**, a result which paves the way to a synthesis of the entire A-B-C-D ring system of castasterone by an IMDA reaction. Results along this line will be reported in due course.

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Notes and References

1- Zoller, T.; Uguen, D.; De Cian, A.; Fischer, J.; Sablé, S. *Tetrahedron Lett.* **1997**, *38*, 3409-3412.

2- Zoller, T.; Uguen, D. *Eur. J. Org. Chem.*. **1999**, 1545-1550.

3- See following paper.

4- The results reported herein are taken in parts from the Doctorate dissertation of T. Z. (Strasbourg, 1998). All new compounds have been fully characterised by NMR (^{1}H, ^{13}C, ^{1}H-^{13}C correlation, COSY, NOESY, HMBC), mass, and I. R. spectroscopies, and by elemental analysis (C, H). In one case (**3b**), the assigned structure has been confirmed by a single crystal X-ray analysis (to be published elsewhere). *Selected data*: **3b**: Colourless crystals, m. p. 205-206 °C (nitromethane/H_2O); **3c**: oil; ^{13}C NMR ($CDCl_3$): 21.2, 26, 26.6, 27.6, 34.9, 38.5, 40.2, 41.7, 46.2, 47.3, 51.8, 60.9, 123, 134.9, 173.8, 211.2; **3d**: oil; ^{13}C NMR: 21.4, 26.1, 26.2, 26.5, 26.7, 28.9, 35.1, 37.4, 40.5, 43.8, 53.3, 124.1, 127.2, 129, 132.2, 135.3, 138.8, 214; **3e**: Pale-yellow solid, m.p. 148-149 °C; **8**: White solid, m. p. 133-134 °C; ***CAT*-9**: White solid, m. p. 132-133 °C; ***TAT*-9**: White solid, m. p. 158-159 °C; **10**: oil; ^{1}H NMR (200 MHz, $CDCl_3$): 0.7 (t, J=4.5 Hz, 1H), 0.94 (s, 3H), 0.99-2.05 (m, 17H), 2.42 (dd, J=16, 3.5 Hz, 1H).

5- Previously (see ref. 1 and quoted reference therein), IMDA reaction of the *E* isomer of compound **2a** has been shown to proceed via an *endo-chair* transition state to give the *cis-syn-trans* isomer ***CST*-3** .

6- With the keto sulfones **3b** and **3e**, as well as with the keto ester **3c**, the *exo* (vs *endo*) denomination is not obvious: should the sulfonyl and the methoxycarbonyl groups be more efficient than the ketone functionality with regards to the activation of the dienophilic system, the corresponding transition states will be more adequately designated as *endo-chair*. However, literature data dealing with the *intermolecular* Diels-Alder reaction of related β-sulfonyl- and β-alcoxycarbonyl-vinylketone strongly suggest that the dominant directional effect is developed by the ketone functionality (see, for instance: Leon, F. M.; Carretero, J. C. *Tetrahedron Lett.* **1991**, *32*, 5405-5408).

7- Parker, W. L.; Woodward, R. B. *J. Org. Chem.* **1969**, *34*, 3085-3089.

8- Aburatani, M.; Takeuchi, T.; Mori, K. *Synthesis* **1987**, 181-183.