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# TRANSANNULAR CYCLISATION OF GERMACRONE AND ISOGERMACRONE VIA OXYMERCURATION–DEMERCURATION

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**Abstract**—Germacrone **1** undergoes transannular cyclisation by OM–DM yielding the *trans*-decalin derivatives **3**, **4** and **5**. Isogermacrone **2** similarly yields **3**, **4** and **5** and, as a minor product, the ketone **8**. The stereochemistry and the mechanism of the intramolecular olefinic cyclisation are discussed.

The generality and utility of the oxymercuration–demercuration (OM–DM) sequence for the Markovnikov hydration of olefines has been recently emphasised by Brown *et al.*[1] The reaction proceeds via cationic $\pi$-complex which reacts with the nucleophilic agent. If the system contains a second suitably oriented double bond, then it can act as a nucleophilic agent resulting in an olefinic cyclisation. The few reports on the carbocyclisation of cyclodeca-1,5-diene systems by OM–DM demonstrate the high regio- and stereoselectivity of the reaction.[2] Further investigation on this subject should extend the application of electrophilic metal salts for olefinic cyclisations and could give further information on the stereochemistry and the mechanism of the metallation reactions.

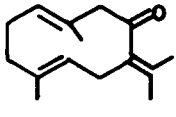
We report some results of the cyclisation of germacrone **1** and isogermacrone **2** by oxymetallation with mercury-II-acetate.

## RESULTS

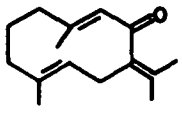
OM–DM of **1** according to Brown's general procedure[1a] afforded a mixture of the ketol **3** (70%) and the isomeric ketones **4** and **5** (a total of 15%). The structure and stereochemistry of **3** follow from the spectral data and chemical transformations. The mass spectrum shows the chemical composition $C_{15}H_{24}O_2$ ($M^+$ 236) and the presence of an OH group ($M^+$-18). The strong UV absorption at 257 nm and the IR bands at 1670 and 1610 $cm^{-1}$ reveal the conjugation of the CO group with the isopropylidene double bond. The NMR signals are consistent with **3**: 0.92 (s, 3 H, $H_{14}$), 1.23 (s, 3 H, $H_{15}$), 1.83 (s, 3 H, $H_{13}$), 2.02 (s, 3 H, $H_{12}$), 2.20 (s, 2 H, $H_9$), 3.01 (dd, J = 15.8, J = 4.0, 1 H, $H_{6\alpha}$), 2.11 (dd, J = 15.8, J = 10.3, 1 H, $H_{6\beta}$). Reduction of **3** with LAH followed by acetylation and hydrogenolysis of the allylic ester group of **6** by Li in liquid ammonia gave the alcohol **7** whose m.p. and spectral data coincided with those of juniper camphor.[3] Since there was a disagreement[4] over the stereochemistry of the latter, the configuration at $C_4$ in **7** was resolved by using the solvent-induced NMR shift correlation of Demarco *et al.*[5] The NMR spectrum of **7** in pyridine showed the $C_{10}$–Me signal at 0.90 $\delta$, whereas in $CDCl_3$ it appeared at 0.94 $\delta$. Since there is no deshielding effect, a 1,3-diaxial interaction between $C_4$–OH group and $C_{10}$–Me does not exist, i.e. the OH group is equatorial. Moreover, dehydration of **3** with $SOCl_2$ in pyridine yielded a mixture of **4** and **5** in a ratio of 4:1, which could be taken as supporting an equatorial group.[6]

The isomeric ketones **4** and **5** were identified as 5$\alpha$H-selina-4(15),7(11)-diene-8-one[7] and 5$\alpha$H-selina-3,7(11)-diene-8-one[8] on the basis of their spectral properties.

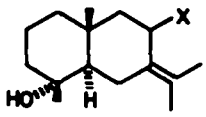
OM of **2** proceeded more slowly—the yellow suspension formed at the start of the reaction took about 2 hr to



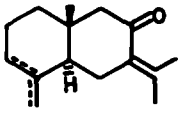
**1**



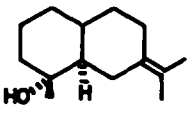
**2**
**12–4,5-epoxide**



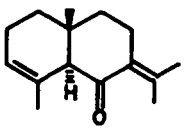
**3** X = O
**6** X = OAc



4–$\Delta^{4,15}$
5–$\Delta^{3,4}$



**7**



**8**

disappear. In spite of the prolonged time of the OM stage, unchanged 2 (*ca* 16%) was isolated from the reaction mixture after DM, alongside with the cyclic products 3, 4 and 5 (65% total). Another ketone, for which the structure 8 was proposed, was also isolated as a minor product (4%). The IR and NMR spectra of 8 are very similar to those of isoacolamone (5α H-selina-3-ene-7β-isopropyl-6-one), recently isolated from *Acorus Calamus L.*[9] The only difference is in the presence of the isopropylidene group conjugated with the CO group which caused the UV absorption at 248 nm and the IR bands at 1690 and 1620 $cm^{-1}$. The lack of absorption at 1420 $cm^{-1}$, and the absence of the NMR signal in the region of 2.20 δ, characteristic for the two $C_9$-protons in 3, 4 and 5, fix the position of the CO group at $C_6$. The NMR data are consistent with 8: 1.0 (s, 3 H, $H_{14}$), 1.67 (s, 3 H, $H_{15}$), 1.77 (s, 3 H, $H_{12}$), 1.93 (s, 3 H, $H_{13}$), 2.62 (s, 1 H, $H_5$), 5.55 (m, 1 H, $H_3$).

## DISCUSSION

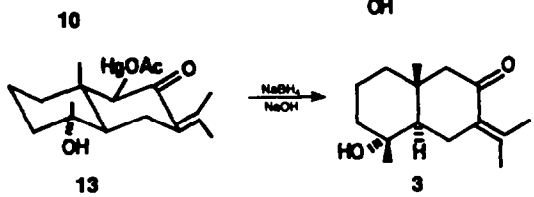
A number of reports[10-13] on electrophil- and radical-induced cyclisation of cyclodeca-1,5-diene derivatives reveal the high regio- and stereoselectivity of the reaction. A preferential attack at 1,10-bond occurs in all cases. In order to explain this fact, Sutherland[2a,10] postulated that the transannular C–C bond formation was synchronous with the C–X formation (X being the nucleophilic reagent). On the basis of the accumulated results, it is concluded that the stereochemistry of the cyclisation products depends on the conformation of the starting cyclodecadienes. The finding that *EE*-1,5-dienes afford *trans*-decalin derivatives whereas *ZE*-1,5-dienes[2b,13] yield *cis*-decalin products demonstrates that the prefered conformation is the one with crossed double bonds giving the lower energy chair-like transition state. Very recently Kodama *et al.*[13] have reported that the *ZZ*-isomer of hedycaryol yields *cis*-decalin products via the parallel conformation. The authors suggest that the compound reacts slowly through the parallel conformation as, in the crossed form, the *p*-orbitals of the *ZZ*-bonds are kept distant from each other and are not suited for the π–π interaction.

The conformation found for germacrone 1 as its silver nitrate complex[12] is the crown 9 with crossed *EE*-double bonds. The structure and stereochemistry of the bicyclic products are to be expected and in accordance with the mechanism proposed by Sutherland. It may be argued that the ketol 3 could have been formed by OM of the isomeric ketones 4 and 5. However OM–DM of 4 and 5 resulted in the unchanged initial compounds.

There are no data about the conformation and stereochemistry of isogermacrone 2. A careful study of the NMR spectrum of 2 revealed a coupling between the methyls and vinylic protons (J = 1.2) which is an indication for the *trans*-configuration of both endocyclic bonds. On the other hand, the Dreiding model of 2 showed a quite flexible molecule. Most probably, in a solution at room temperature, there is an equilibrium between various conformations as indicated by the width and absence of a spin splitting pattern of some of the NMR signals. Within the constraints of the medium-ring, two distinct conformations—10 with parallel and 11 with crossed bonds are possible for the *EE*-1,6-diene unite. Clearly, these different conformations would give different ring-junction stereochemistry. Since the main resulting bicyclic products 3, 4 and 5 are with a *trans*-decalin skeleton, evidently they arise from 10 by attack of the mercury acetate at 9,10 bond. An attack at 4,5-bond accounts for the formation of the minor product 8. The inspection of the Courtauld model of 2 clearly showed that the π–π interaction between the endocyclic bonds in 11 was much smaller than in 10 which could determine 10 as the reacting conformation. On the other hand, 10 would give the lower energy chair-like transition state.

The results of the OM–DM of 2 have shown that the olefinic cyclisation of this cyclodeca-1,6-diene system proceeds also highly regio- and stereoselectively, most probably according to the conserted mechanism with a synchronous formation of carbon-metal and C–C bonds suggested for 1,5-dienes. A significant fact which supports such a mechanism is that epoxidation of 2 gave the isogermacrone-4,5-epoxide 12 only, i.e. an electrophilic reagent not leading to cyclisation attacks the 4,5-bond preferentially.

Thus the OM–DM of 2 should proceed via metallation at the 9,10-bond with a Markovnikov intranucleophilic attack at $C_{10}$ resulting in a carbon-metal bond at $C_9$ (Scheme 1). The following equatorial nucleophilic attack at $C_4$ fully determines the reaction stereospecifity. The reductive DM of the intermediate 13 yields the main cyclisation product 3.



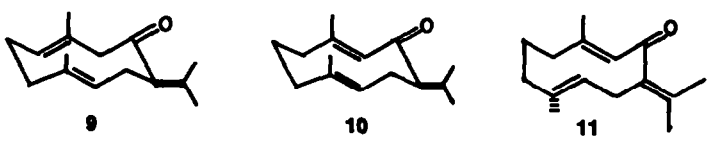

Scheme 1.

## EXPERIMENTAL

M.ps are uncorrected. UV: in EtOH, IR: film or KBr pellets, NMR: in $CDCl_3$ (unless indicated otherwise) at 60, 100 and 200 MHz, chemical shift in δ downfield from TMS, J in c/s. "Work-up in the usual way" implies dilution with water, extraction with ether, washing, drying ($Na_2SO_4$) and removal of the solvent under reduced pressure.

*Germacrone* 1. Isolated from the Bulgarian Zdravetz oil, m.p. 56–57°(EtOH), NMR (200 MHz): 1.44 (d, J = 1.2, 3 H, $H_{15}$), 1.63 (d, J = 1.2, 3 H, $H_{14}$), 1.73 (s, 3 H, $H_{13}$), 1.78 (s, 3 H, $H_{12}$), 2.95 (d, J = 10.5, 1 H, $H_9$), 3.42 (d, J = 10.5, 1 H, $H_9$), 4.72 (ddd, J = 10.7, 4.4, 1.2, 1 H, $H_5$), 4.99 (br d, J = 11.2, 1 H, $H_1$).

*Isogermacrone* 2. Germacrone 1 (1.50 g) was dissolved in EtONa (0.2 g Na in 5 ml EtOH) and was allowed to stand at room



temp. for 12 hr.[14] Crystallisation from EtOH yielded **2** (0.95 g), m.p. 52–54°, NMR (200 MHz): 1.52 (d, J = 1.2, 3 H, $H_{15}$), 1.68 (d, J = 2.2, 6 H, $H_{12}$ and $H_{13}$), 1.82 (d, J = 1.2, 3 H, $H_{14}$), 2.90 (m, 2 H, $H_6$), 5.16 (td, J = 7.9, 8.7, 1.2, 1 H, $H_5$), 6.01 (d, J = 1.2, 1 H, $H_9$).

*OM–DM of* **1**. A soln of **1** (1.09 g, 5 mM) in 10 ml THF was added dropwise to a stirred yellow suspension of $Hg(OAc)_2$ (1.60 g, 5 mM) in aqueous THF (25 ml of each solvent). The yellow colour disappeared within 30 min. The mixture was stirred further 30 min. NaOH soln (3 M, 3 ml) and $NaBH_4$ soln (0.1 g in 25 ml 3 M NaOH) were added dropwise, the black suspension was stirred for 1 hr and worked up in the usual way to give an oil (0.85 g) which was chromatographed over $SiO_2$ (80 g). Elution with 2:1 hexane–ether gave fraction A (0.15 g). Elution with EtOAc gave the *ketol* **3** (0.65 g), m.p. 112–114° (1:2 hexane–ether), for UV, IR and NMR (100 MHz) data, see the initial section. Chromatography of fraction A over $SiO_2/AgNO_3$ (20 g) and elution with petroleum ether–ether (5:1 and 3:1) afforded the *ketone* **4** (70 mg), oil, $\lambda_{max}$ 254 nm, $\nu_{max}$ 1680, 1640, 1620, 890 $cm^{-1}$, NMR (60 MHz): 0.80 (s, 3 H, $H_{14}$), 1.86 (s, 3 H, $H_{13}$), 2.00 (s, 3 H, $H_{12}$), 2.30 (s, 2 H, $H_9$), 4.65 and 4.86 (br s, each 1 H, $H_{15}$), and the *ketone* **5** (50 mg), oil, $\lambda_{max}$ 254 nm, $\nu_{max}$: 1675, 1615, 808, 751 $cm^{-1}$, NMR (60 MHz): 0.86 (s, 3 H, $H_{14}$), 1.71 (s, 3 H, $H_{15}$), 1.84 (s, 3 H, $H_{13}$), 2.09 (s, 3 H, $H_{12}$), 2.22 (s, 2 H, $H_9$), 5.43 (br s, 1 H, $H_3$).

*Alcohol* **7**. The monoacetate **6** (240 mg) obtained by reduction of **3** (250 mg) with LAH and following acetylation ($Ac_2O$/Py) was dissolved in fresh distl dry THF (6 ml) and added dropwise to a stirred soln of Li (0.2 g) in liq $NH_3$ (70 ml). The mixture was stirred further for 1 hr and solid $NH_4Cl$ was added until it completely decoloured the soln. After evaporation of the ammonia, usual work-up and purification of the crude product on preparative tlc yielded **7** (170 mg), m.p. 166–167°(EtOH), $\nu_{max}$: 3420, 1385, 1105, 910 $cm^{-1}$, NMR (60 MHz): 0.94 (s, 3 H, $H_{14}$), 1.15 (s, 3 H, $H_{15}$), 1.68 (s, 6 H, $H_{12}$ and $H_{13}$), in pyridine: 0.90 (s, $H_{14}$), 1.17 (s, $H_{15}$), 1.65 (s, $H_{12}$ and $H_{13}$).

*Dehydration of* **3**. The ketol **3** (100 mg) was dehydrated with $SOCl_2$ (0.5 ml) in pyridine (5 ml) at 3°. Work-up in the usual way gave an oil (85 mg) which was chromatographed over $SiO_2/AgNO_3$ (15 g). Elution with petroleum ether–ether (5:1 and 3:1) yielded **4** (60 mg) and **5** (15 mg).

*OM–DM of* **2**. A soln of **2** (1.09 g, 5 mM) in 10 ml THF was treated with $Hg(OAc)_2$ (1.60 g, 5 mM) as above. The yellow colour disappeared within 2 hr. After further stirring for 2 hr and DM ($NaBH_4$/NaOH) the mixture was worked up in the usual way. Chromatography of the crude product over $SiO_2$ and $SiO_2/AgNO_3$ afforded **3** (360 mg), **4** (65 mg), **5** (40 mg), **2** (140 mg) and **8** (35 mg), oil, for UV, IR, NMR (60 MHz) data, see the initial section.

*Isogermacrone-4,5-oxide* **12**. To a soln of **2** (300 mg) in $CHCl_3$ (10 ml) was added a soln of *m*-Cl-perbenzoic acid (210 mg) in $CHCl_3$ (5 ml) at 0°. The mixture was kept overnight at 5° and worked up in the usual way. Preparative tlc of the crude product (285 mg) afforded unchanged **2** (190 mg) and **12** (80 mg), m.p. 78–80° (EtOH), NMR (100 MHz): 1.00 (s, 3 H, $H_{15}$), 1.60 (s, 3 H, $H_{13}$), 1.75 (s, 3 H, $H_{12}$), 1.91 (s, 3 H, $H_{14}$), 2.53 (m, 1 H, $H_5$), 2.80 (m, 2 H, $H_6$), 5.43 (s, 1 H, $H_9$).

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