259. Regio- and Stereoselective Functionalizations of Tricyclo[3.3.0.0^{2,8}]octan-3-one, a Potential Synthon for Polycyclopentanoid Terpenes and Prostacyclin Analogs

Preliminary Communication[1])

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(29.IX.80)

Summary

Chemical transformations of tricyclo[3.3.0.0^{2,8}]octan-3-one (**1**) have been carried out in order to explore its potential utility as a versatile synthon for polycyclopentanoid terpenes and prostacyclin analogs. Various functionalizations of rings A and B and annulation of a third ring C were achieved in generally high yields. The system provides for a large measure of regio- and stereoselective reaction control.

Introduction. – In the preceding communication [3] we described a facile and high-yield synthesis of tricyclo[3.3.0.0^{2,8}]octan-3-one (**1**) and its methyl homologs **2** and **3**, and the resolution of **1** into the pure enantiomers. Chemical transformations of **1** are now reported, which aim at the exploration of **1** as a synthon for polycyclopentanoid compounds such as 9(O)-methanoprostacyclin (**4**), the pentalenolactone family (*cf.* **5**), and the coriolins (*cf.* **6**)[2]). In particular, syntheses of the following intermediates have been achieved: (*i*) **9** in 67%, **12a** in 79% and **12b** in 55% overall yield from **1** (s. *Scheme 2*), all three possessing oxygen functions in ring A; (*ii*) **13** in 96%, **15** in 60% and **16** in 31% yield *(Scheme 4)*, the ring B of **15** and **16** being alkylated and enlarged to a six-membered lactone; and (*iii*) **20** in 59% yield *(Scheme 5)* with a ring C annulated.

Functionalization of ring A. – Ring opening of the cyclopropyl ketone moiety proved a smooth approach to functionalize ring A of **1** when assisted by coopera-

[1]) Presented in parts at the ESOC I Conference, Köln 1979 [1], and in full at the VIII IUPAC Symposium on Photochemistry, Seefeld 1980 [2].

[2]) For the most recent contributions to the rapidly growing list of syntheses in this field, see [4] for **4**, [5] for **5**, and [6] for **6**.

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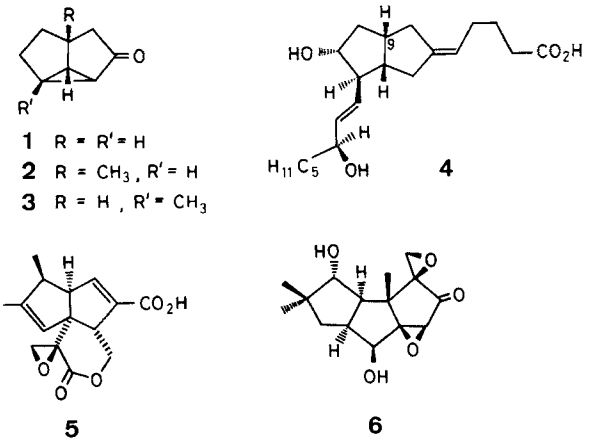
Scheme 1. *Synthons* **1–3** *[3] and representative examples of potential target compounds*



tive electrophile and nucleophile action[3]). Methyl and trimethylsilyl trifluoromethanesulfonates[4]) readily isomerized **1** to **7**[5]) *(Scheme 2)* in chloroform at room temperature. According to GLC. the transformation was clean and nearly quantitative in both cases, but the yields dropped to 50% after chromatographic purification of the reaction product. However, when the reaction was conducted for 18 h in refluxing benzene with 20% (*w/w*) of the polymer-supported silylating agent *Nafion*-TMS [10][7]), **7** was isolated in >95% yield after filtration of the *Nafion* polymer and distillation of the crude product at 65°/1 Torr[8]).

The potential carbocation **a** *(Scheme 3)*, formed by electrophilic opening of the cyclopropyl ketone **1** by *El*, has two options to react with a nucleophile *Nu*. Proton elimination and protolytic cleavage of the enoxy moiety has been encountered in the case of **1**→**7**, and direct addition of nucleophiles (path *ii*→**c**) has been described earlier [12] (see also below and *Scheme 4:* **13**→**14a/b**). It is doubtful, however, that the formation of **7** proceeds *via* **b** (path *i*). No such intermediate could be detected even in the presence of proton scavengers like 1,5-diazabicyclo[4.3.0]non-5-ene or carbonate. Moreover, facile hydrolysis of **b** with $El = CH_3$ is unlikely. One may speculate that the electron-rich double bond of **a** ($El = CH_3$, $(CH_3)_3Si$) could act as a (possibly internal) nucleophile for proton abstraction from C(7), leading directly from **a** to **7** (path *iii*).

Two key transformations of the unsaturated ketone **7** were subsequently elaborated. Firstly, oxidation of the unsaturated ring A, accompanied by reclosure to the tricyclooctanone skeleton (→**9**), was designed to serve as a route to coriolin

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[3]) An attempt failed to directly oxidize ring A and form the 3,7-diketone by the action of ozone on **1** when adsorbed on silica gel [7].

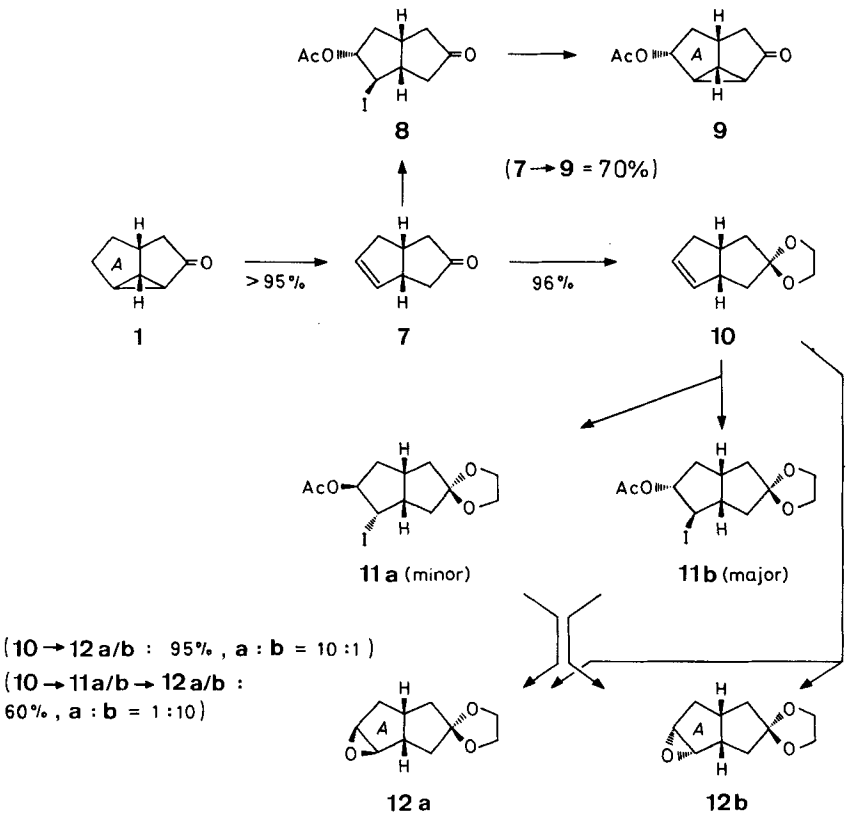
[4]) See [8] for a cyclopropyl ketone cleavage by another *Mazur*-type [9] reagent, trimethylsilyl trifluoroacetate, which, however, was followed by a deep-seated skeletal rearrangement.

[5]) Satisfactory analytical data were obtained for all new compounds. They will be reported in the full publications.

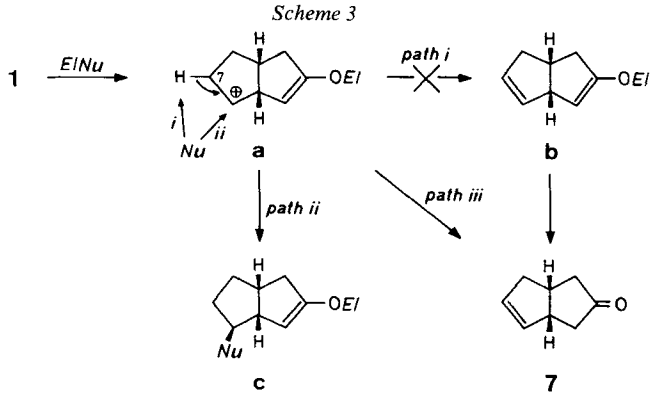
[7]) We are grateful to Professor *R. Noyori* for a generous gift of *Nafion*-TMS, which is the silylated form of a perfluorinated resin sulfonic acid.

[8]) The unsaturated ketone **7** has previously been synthesized in much lower yield *via* a different route [11].

Scheme 2. *Functionalization of ring A*[6])



Scheme 3



ElNu in path *ii* = $CH_3SO_2OCOCH_3 + Br^-$ or I^- [12]

ElNu in path *iii* = $CF_3SO_2OCH_3$, $CF_3SO_2OSi(CH_3)_3$, *Nafion*-TMS

[6]) All compounds in the *Schemes 2, 4* and *5* are racemic.

(**6**). Secondly, *endo*-epoxidation (→**12b**) should provide an access to the 9(O)-methanoprostacyclin (**4**) group. Both objectives were achieved, as described in the following, with *Prévost* reactions which proceded with high regio- and stereoselective control[9]).

When **7** was treated for 24 h in boiling benzene with two equivalents of silver acetate and one equivalent of iodine, one major product (**8**; GLC.: 80–85%) was formed which decomposed on attempted isolation. Therefore, the crude reaction mixture, after filtration, was directly treated for 3 h at room temperature with excess diazabicyclononene affording the tricyclic acetoxy ketone **9** in 70% overall yield after chromatography on silica gel. The configurational assignments of **8** and **9** are based on the facile ring closure which would not be expected of the stereoisomeric *Prévost* product, and, furthermore, on analogy with the predominating steric course of the reaction **10**→**11a/b** (see below).

Acetalization of **7** with ethylene glycol, methyl orthoformate, and *p*-toluenesulfonic acid in ether at room temperature gave compound **10** in 96% yield *(Scheme 2)*. Under the same *Prévost* conditions as above, **10** afforded a mixture of the acetoxy iodides **11a/b** which were only moderately stable at room temperature. With potassium carbonate in methanol they were converted to the epoxides **12a** and **12b** (ratio 1:10) which were separated on *florisil* (60–100 mesh). The overall yield from **10** was 55% of isolated **12a** and **12b**. Epoxidation of **10** with *m*-chloroperbenzoic acid, the direct route to **12a/b**, proceded with the inverse stereoselectivity, albeit with a total yield of 95% of separated isomers.

The epoxide configuration of **12a** and **12b** is indicated by the stereoselectivity of the epoxidation which must preferentially occur from the less hindered *exo* side (→**12a**). The result of a 270-MHz-^{1}H-NMR. study with Eu(fod)$_3$ shift reagent in chloroform confirmed this assignment. The proton signals of the *exo* epoxide **12a** (*d* at δ 3.37 and $d \times d$ at δ 3.52) shift more strongly downfield with added Eu(fod)$_3$ than did the signals of the *endo* epoxide **12b** (2 broad signals at δ 3.44 and 3.59). Clearly, the difference between the two isomers will residue in a greater influence on the *endo* protons of **12a** by the europium salt complexed with the *endo* O-atom of the acetal moiety.

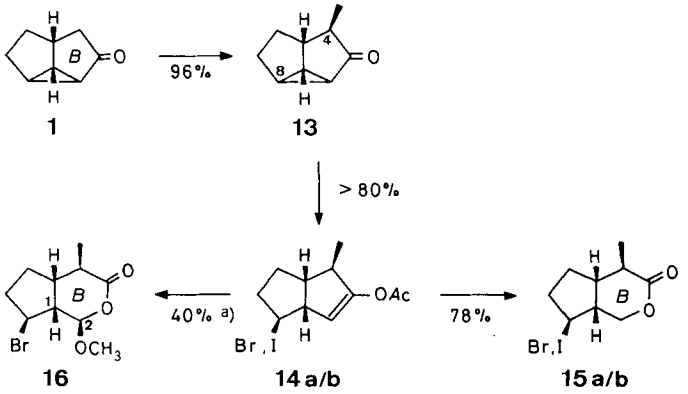
Functionalization of ring B. – Treatment of **1** for 4 h with methyl iodide and sodium hydride in boiling tetrahydrofuran containing 1% of hexamethylphosphotriamide gave in a stereoselective *exo* alkylation 96% of **13** *(Scheme 4)*[10]). Homologous C(4)-dimethylated material (2%) was readily removed by chromatography after the subsequent steps. On exposure of **13** to acetyl methanesulfonate [9] and tetramethylammonium halide in acetonitrile, S_N2-type cyclopropane cleavage with addition of the nucleophile Br^- or I^- at C(8) was accompanied by regiospecific enolate trapping furnishing **14a** and **14b**, respectively, in >80% yield each.

Ring B was enlarged to a six-membered lactone by oxidative cleavage of **14a** and **14b** with osmium tetroxide/sodium periodate in aqueous dioxan, reduction with sodium borohydride in methanol, and hydrochloric-acid-catalyzed ring closure. The halolactones **15a** and **15b**, respectively, were thus obtained in 78%

[9]) A similarly high selectivity of a *Prévost* reaction was reported for a lactone analog of **7** [13].

[10]) A non-selective synthesis of **13** has recently been reported [14].

Scheme 4. *Functionalization of ring B*[6])



a) Yield after recrystallization, not optimized.

yield each and in 99% purity (GLC.). The structure of the bromolactone **15a** was established by a single crystal (m.p. 103–104°, from ethyl acetate) X-ray crystallographic diffraction analysis[11]).

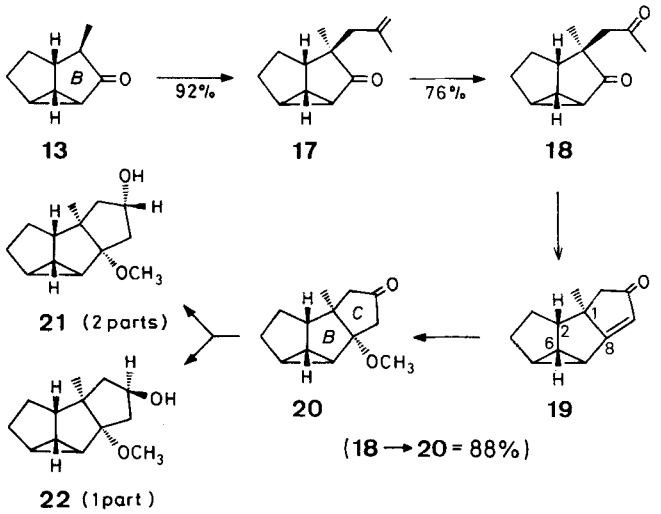
When **14a** was subjected to a sequence of ozonolysis (in methanol/methylene chloride at −78°), borohydride reduction and acidification, a single product **16** was isolated (m.p. 109–110°; from ethyl acetate/hexane). The methoxy group in **16** obviously originates from the methanol-assisted cleavage of the ozonide [15], which leads in steps to a methoxyhydroperoxide, by reduction to the hemiacetal, and with acid to the methoxylactone. The β-configuration of the methoxy substituent of **16** is indicated by a vicinal ^{1}H-NMR. coupling constant of 8 Hz for H–C(2). This value would be expected for a dihedral angle of *ca.* 180° between H–C(1) and H–C(2), as it is possible with an equatorial β-configurated methoxy group, but would appear incompatible with an angle in the range of 60° imposed by the 2α-stereoisomer.

Annulation of ring C. – Ketone **13** was treated for 24 h with 2-methylallyl bromide (2-methylallyl chloride and potassium bromide) and potassium *t*-butoxide in boiling *t*-butyl alcohol/benzene to give **17** in 92% yield *(Scheme 5)*. The assignment of the *exo* configuration of the methylallyl substituent is mandatory in view of the necessarily strong stereocontrol exerted by the basket-like skeleton of the enolate form of **13**, and the high yield of a homogeneous reaction product[12]). Oxidative double-bond cleavage by osmium tetroxide/sodium periodate in aqueous tetrahydrofuran at room temperature and chromatographic purification on silica gel afforded a 76% yield of **18** (GLC.: 99% purity). Finally, cyclization of this diketone by treatment with potassium *t*-butoxide/potassium hydroxide in boiling methanol for 48 h gave the tetracyclic product **20** in 88% yield. The intermediate enone **19** proved to be sufficiently reactive towards nucleophilic addition to escape attempts of isolation.

[11]) Unpublished result by *L. K. Liu & C. Krüger, Max-Planck*-Institut für Kohlenforschung.

[12]) Stereoselectivity should be even more compelling here than in the case of methylallyl substitution of bicyclo[3.3.0]octan-3-one [16].

Scheme 5. cis-*1*-transoid-*1,2*-cis-*2*-*Tetracyclo[6.3.0.0^{2,6}.0^{5,7}]undecane skeleton by ring C annulation*[6])



The *cis* fusion of rings B and C of **20** was demonstrated as follows. Lithium aluminium hydride reduction of **20** in ether at 0° quantitatively gave a 2:1 mixture of **21** and **22**, with which ^{1}H-NMR. experiments with increasing concentrations of the shift reagent Eu(fod)$_3$ were carried out. The signals of the 1-methyl (at 0.80 ppm for **22** and 0.91 ppm for **21**) and the 8-methoxy group (at 3.34 ppm for **22** and 3.36 ppm for **21**) responded pairwise within each product with similar down-field shifts, with much larger shifts in **21**. This result shows that the two angular substituents have a *cis* orientation.

K.N. thanks the Japanese Ministry of Education for a fellowship.

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