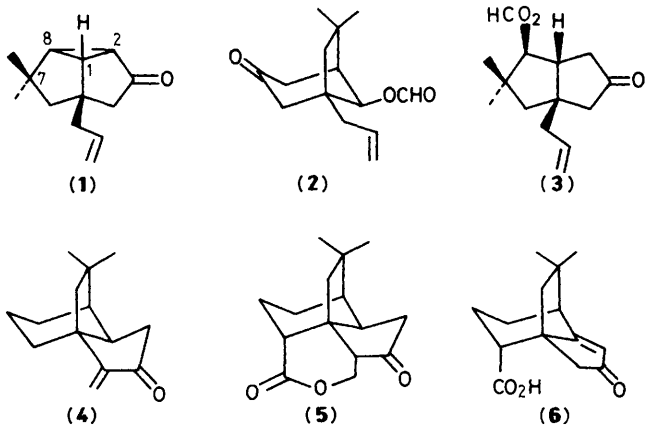
Anomalous Transformation of Tricyclo[3.3.0.0^{2,8}]octan-3-ones into Bicyclo[3.2.1]octan-3-ones, a Novel Route to (±)-Quadrone

Takeshi Imanishi, Munetaka Matsui, Masayuki Yamashita, and Chuzo Iwata*

Faculty of Pharmaceutical Sciences, Osaka University, 1—6 Yamadaoka, Suita, Osaka 565, Japan

A novel route to (±)-quadrone (**5**) has been developed *via* an anomalous C(1)–C(2) bond cleavage of 4-benzyloxymethyl-7,7-dimethyl-3-oxotricyclo[3.3.0.0^{2,8}]octane-5-acetic acid (**11**) by an intramolecular participation of the carboxy group.

Tricyclo[3.3.0.0^{2,8}]octan-3-one compounds are known to undergo ready cleavage of the C(2)–C(8) bond under substitution or reduction conditions.[1] This reaction has been frequently utilized as a key step in the synthesis of many natural products.[2] To the best of our knowledge, however, there have been no reports concerning the predominant cleavage of the C(1)–C(2) bond. We envisaged a new synthetic route to bicyclo[3.2.1]octanones starting from easily available tricyclo[3.3.0.0^{2,8}]octan-3-ones *via* an anomalous cleavage of the C(1)–C(2) cyclopropane bond. We have already reported that a tricyclo[3.3.0.0^{2,8}]octan-3-one (**1**) having C(7) *gem*-dimethyl groups afforded the bicyclo[3.2.1]octanone product (**2**) along



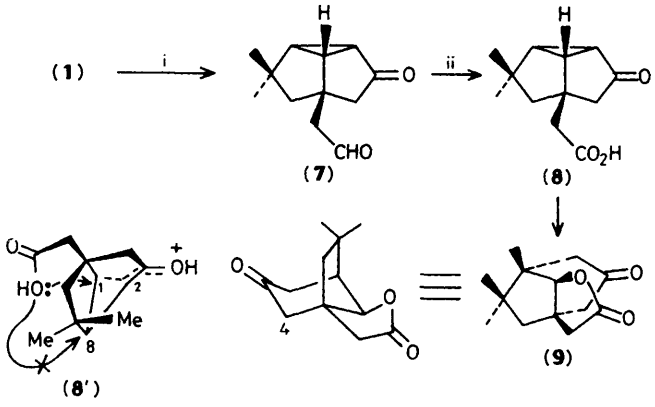
with by-product (**3**) on treatment with formic acid. This result, which was successfully applied to the total synthesis of (±)-decarboxyquadrone (**4**),[3] is attributable to a steric requirement. Unfortunately, this procedure was found to be unsuitable for synthesis of quadrone (**5**)[4,5] itself.

We describe here a simple method for exclusive C(1)–C(2) bond cleavage of the tricyclo-octanone ring system utilizing the participation of an intramolecular carboxy group, and also its successful application to a synthesis of the carboxylic acid (**6**), a known synthetic intermediate[5a] for quadrone (**5**).

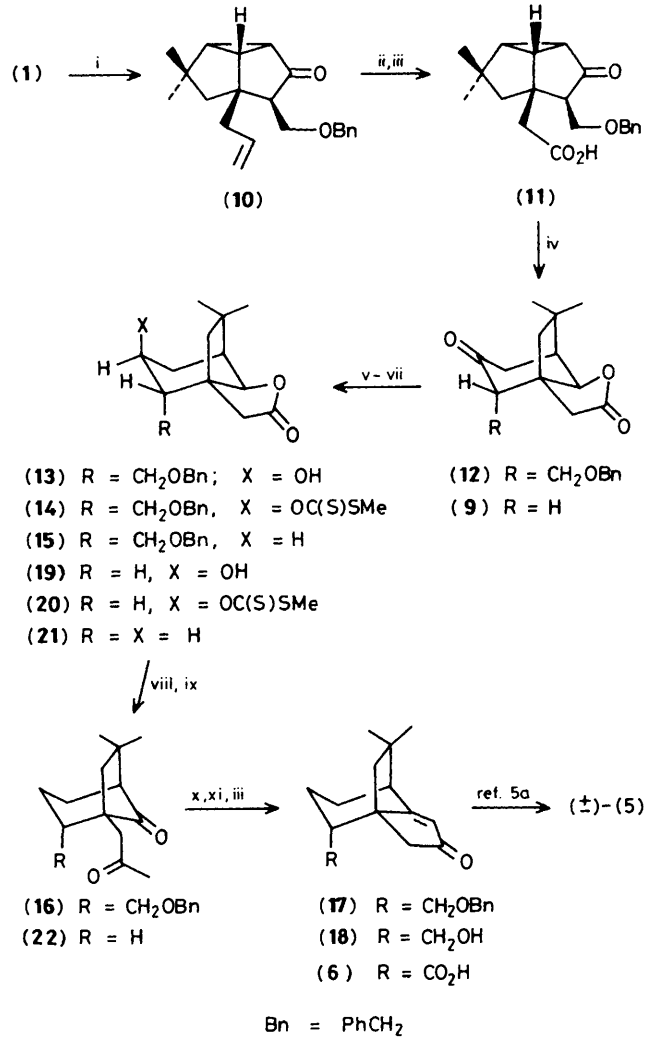
Ozonisation of (**1**) followed by treatment with dimethyl sulphide provided the aldehyde (**7**),† which was oxidized to the carboxylic acid (**8**), m.p. 88—91 °C, in 55% yield. On heating (**8**) with a catalytic amount of toluene-*p*-sulphonic acid (TsOH) in benzene, the desired product (**9**), m.p. 184—185.5 °C, was obtained in 98% yield. The i.r. spectrum exhibited a strong absorption band characteristic of the γ-lactone carbonyl at 1785 cm^{-1}. Thus the observed exclusive cleavage of the C(1)–C(2) cyclopropane bond could be interpreted as follows. The carboxy group can easily approach the C(1) position but is distant from the C(8) centre. A combination of increasing the electrophilicity of the cyclopropane moiety by protonation of the ketone, and the desired situation of the internal nucleophile (the carboxy group), results in the exclusive cleavage of the C(1)–C(2) bond of (**8**) to yield (**9**) *via* the intermediate (**8'**) as shown in Scheme 1.

For synthesis of quadrone, it is necessary to introduce stereoselectively one more carbon unit at C(4) of the lactone (**9**). The problem was solved by a direct alkylation of the starting material (**1**). Exposure of (**1**) to 1.2 equiv. of lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C followed by treatment with 1.5 equiv. of benzyloxymethyl chloride[6] afforded (**10**) in 83% yield as a single diastereoisomer.[7] On ozonisation, reduction, and oxidation, (**10**) was converted into the carboxylic acid (**11**), m.p. 117—118.5 °C, in 61% overall yield. On treatment with TsOH, (**11**) also afforded the γ-lactone (**12**), m.p. 103—104.5 °C, in 94% yield. Sodium borohydride reduction of (**12**) afforded the alcohol (**13**) in 98% yield. Reaction of (**13**) with carbon disulphide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene[8] (DBU) in *N*,*N*-dimethylformamide (DMF) followed by treatment with methyl iodide provided the xanthate (**14**), m.p. 119—121 °C, which was reduced with tri-n-butyltin hydride–2,2'-azoisobutyronitrile[9]

† All new substances exhibited i.r., ^1H n.m.r. (90 or 500 MHz), and mass spectral data consistent with the assigned structure and possessed satisfactory combustion or high resolution mass spectral analytical data.



Scheme 1. *Reagents and conditions*: i, O_3, MeOH, −78 °C; then Me_2S, 25 °C; ii, Jones oxidation, 0 °C; iii, TsOH, C_6H_6, 30 °C.



Scheme 2. *Reagents and conditions*: i, LDA, THF, −78 °C; then $PhCH_2OCH_2Cl$, −78 °C to 0 °C; ii O_3, CH_2Cl_2, −78 °C; then Zn, AcOH, 0 °C; iii, Jones oxidation, 0 °C; iv, TsOH, C_6H_6, 50 °C; v, $NaBH_4$, MeOH, 0 °C; vi, DBU, CS_2, DMF, 50 °C; then MeI, 25 °C; vii, Bu^n_3SnH, AIBN, C_6H_6, reflux; viii, MeLi, THF, 0 °C; ix, PCC, CH_2Cl_2, 25 °C; x, Bu^tOK, Bu^tOH, reflux; xi, Me_2S, $BF_3 \cdot Et_2O$, 25 °C.

(AIBN) to (**15**), m.p. 55—56 °C, in 80% yield. In order to open the lactone ring, (**15**) was treated with methyl-lithium in ether[10] and then oxidised with pyridinium chlorochromate (PCC) in CH_2Cl_2 to give the diketone (**16**) in 77% yield. Facile intramolecular aldol condensation of (**16**) ensued upon treatment with potassium t-butoxide in t-butyl alcohol providing the desired cyclopentenone (**17**) in 60% yield. Debenzylation [Me_2S–BF_3 complex[11]] of (**17**) gave the alcohol (**18**) [87% yield (98% yield based on the consumed starting material)], which was oxidised to the target carboxylic acid (**6**), m.p. 143—148 °C, in 96% yield. This product proved to be identical with an authentic specimen of (**6**) by t.l.c. and spectroscopic analysis. Since the carboxylic acid (**6**) has already been transformed into (±)-quadrone by Danishefsky *et al.*,[5a] the present synthesis of (**6**) constitutes a formal total synthesis of (±)-quadrone. In addition, the γ-lactone (**9**) was also transformed into the diketone (**22**),[3] a synthetic intermediate for (±)-decarboxyquadrone (**4**), *via* intermediates (**19**)—(**21**) as shown in Scheme 2.

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