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A NOVEL CONSTRUCTION OF OCTAHYDRO-3a,7-ETHANO-3aH-INDENE SKELETON FROM A TRICYCLO[3.3.0.$0^{2,8}$]OCTANE: A TOTAL SYNTHESIS OF (±)-DESCARBOXYQUADRONE

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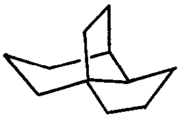
Summary: Total synthesis of (±)-descarboxyquadrone was achieved *via* a regioselective C_1-C_2 bond cleavage of 7,7-dimethyl-5-(2-propenyl)-tricyclo[3.3.0.$0^{2,8}$]octan-3-one as a crucial step.

A novel carbon skeleton, octahydro-3a,7-ethano-3aH-indene (**1**), has been receiving much attention of synthetic organic chemists since quadrone (**2**) was isolated as a metabolite of the fungus *Aspergillus terreus* and was found to show a significant antitumor activity in 1978.[1] More recently new antibiotics, terrecyclic acid A (**3**)[2a] and terrecyclol (**4**),[2b] were characterized as its structural and biologically active congeners. Furthermore, descarboxyquadrone (**5**) which was first synthesized by A.B. Smith, III *et al*. was known to have a similar biological activity to quadrone.[3] Numerous synthetic approaches to this new family have appeared in literatures to date.[4] In this communication we wish to describe a novel synthetic route to this family, illustrated by a synthesis of (±)-descarboxyquadrone (**5**), by means of C_1-C_2 bond cleavage of a tricyclo[3.3.0.$0^{2,8}$]octan-3-one (**6**) as a crucial step.



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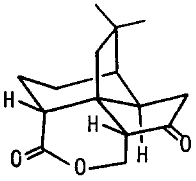

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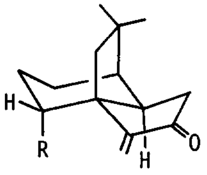
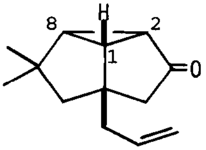
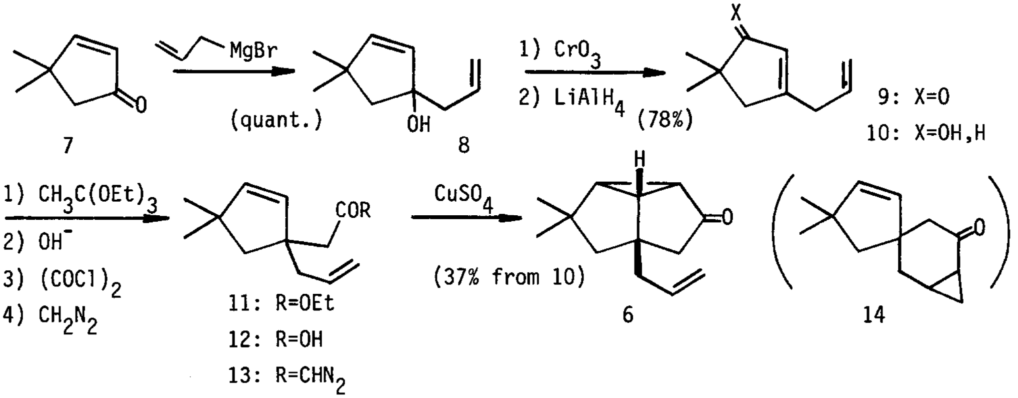


3: R=COOH
4: R=CH_2OH
5: R=H

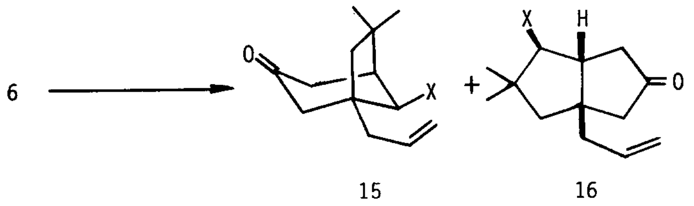


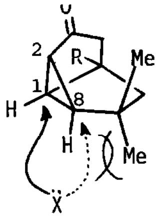
6

The tricyclo[3.3.0.$0^{2,8}$]octane intermediate (**6**) was prepared as follows. The cyclopentenone (**7**)[5] was reacted with allylmagnesium bromide in ether to give exclusively the 1,2-adduct (**8**), which was oxidized with a CrO_3 reagent[6] to the enone (**9**). On treatment with lithium aluminum hydride in ether **9** provided the alcohol (**10**), which was subjected to the orthoester Claisen rearrangement using triethyl orthoacetate in the presence of hydroquinone to give the ester (**11**). Alkaline hydrolysis of **11** afforded the carboxylic acid (**12**) which was converted into the diazoketone (**13**) by the usual way. Heating **13** in cyclohexane in the presence of cupric sulfate provided the desired product (**6**)[7] without any amount of the structural isomer (**14**).[8]



In general, the C_2-C_8 bond of the cyclopropane ring in tricyclo-[3.3.0.0^{2,8}]octan-3-one compounds was found to cleave more easily than the C_1-C_2 bond owing to overlapping between the C_2-C_8 σ bond and the adjacent C=O *p*-orbital.[9,10] However, the geminal dimethyl group at C-7 in the compound **(6)** should prevent the S_N2 attack of nucleophiles to C-8 center as shown in figure **6'** and therefore it is expected that the C-1 center is more rapidly attacked. In fact, under various reaction conditions for cyclopropane ring cleavage in **6** moderate amounts of the 1,2-bond cleaved products **(15)**[7] were mainly obtained along with the 2,8-bond cleaved products **(16)**[7]. The results are summarized in Table.[11] This is the first example of predominant C_1-C_2 bond cleavage in a tricyclo[3.3.0.0^{2,8}]octan-3-one ring system.

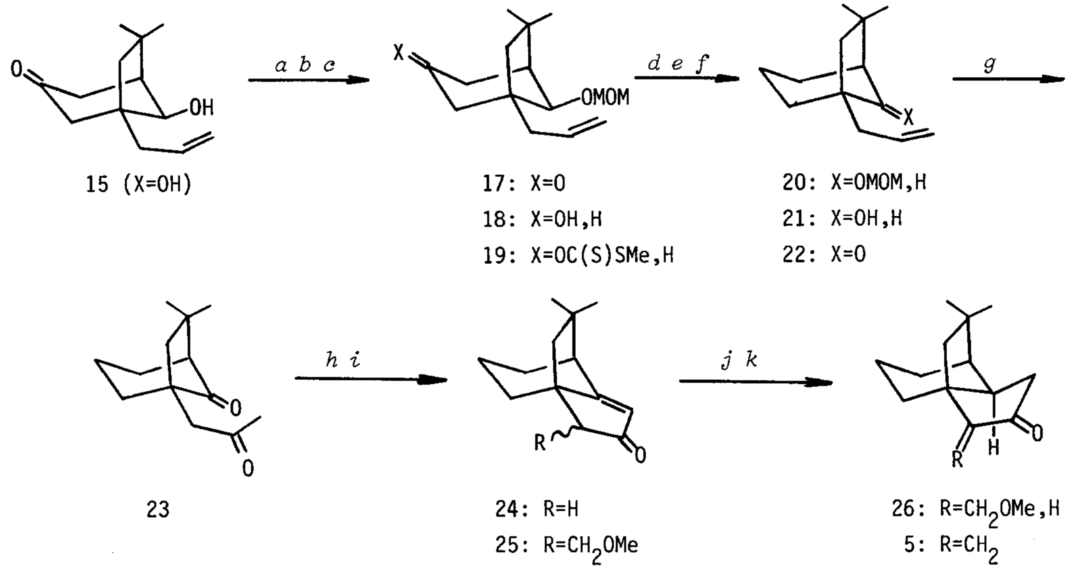




6'

Run	Conditions	X	Yield (%)[a)	
			15	16
1	Li/NH_3 -78°C → refl.	H	—	60
2	c.H_2SO_4-MeOH r.t.	OMe	60	19
3	1) HCOOH 90°C 2) OH^-	OH	25	22
4	1) p-TsOH-HCOOH 80°C 2) OH^-	OH	29	20
5	1) c.H_2SO_4-HCOOH 90°C 2) OH^-	OH	43	20
6	p-TsOH-C_6H_5COOH/C_6H_6 refl.	OTs	43	9
7	TMSCl-NaI/CH_2Cl_2 r.t.	I	70[b)	6[b)
8	AcOMs-Me_4NBr/CH_3CN r.t.	Br	70	trace

a) Isolated yields. b) Yields calculated by means of GLC.



15 (X=OH)

17: X=O
18: X=OH,H
19: X=OC(S)SMe,H

20: X=OMOM,H
21: X=OH,H
22: X=O

23

24: R=H
25: R=CH_2OMe

26: R=CH_2OMe,H
5: R=CH_2

Reagents *a* MOMCl,*i*-Pr_2NEt *b* $NaBH_4$ *c* NaH,CS_2,imidazole;then MeI *d* *n*-Bu_3SnH,AIBN *e* H_3O^+ *f* Jones oxid. *g* O_2,CuCl,$PdCl_2$ *h* $KOBu^t$ *i* LDA;then MOMCl *j* H_2,Pd-C *k* *p*-TsOH

Transformation of **15** (X=OH) into (±)-descarboxyquadrone (**5**) was achieved as follows. Protection of the hydroxy group in **15** (X=OH) as MOM ether followed by $NaBH_4$ reduction of the formed **17** gave **18** in 75% yield. Removal of the hydroxy group in **18** was accomplished by initial derivation to the xanthate (**19**) and subsequent reduction with n-Bu_3SnH in the presence of AIBN[12] to furnish **20** in 71% yield. The alcohol (**21**), obtained in 77% yield from **20** by an acidic hydrolysis, was oxidized to the ketone (**22**; 75%), which was subjected to the Wacker oxidation to give the diketone (**23**)[7] in 69% yield. The enone (**24**),[7] obtained from **23** according to the known method [t-BuOK/t-BuOH],[3a] was allowed to react with MOM-Cl in the presence of 2.2 equiv. of LDA in THF at -78°C → r.t. to afford **25**[7] in 65% yield. Finally, hydrogenation of **25** over 5% Pd-C in methanol to **26** was followed by treatment with p-TsOH in benzene at 45°C to furnish (±)-descarboxyquadrone (**5**)[7] in 85% yield. The synthetic product was proved to be identical with an authentic sample[3a] by spectral comparison (IR and ^{1}H-NMR).

ACKNOWLEDGEMENT We are grateful to Prof. A.B. Smith, III, University of Pennsylvania, for providing spectral copies of (±)-descarboxyquadrone.

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6. *cf*. G. Büchi and B. Egger, J. Org. Chem., **36**, 2021 (1971); S. Wolff and W.C. Agosta, Tetrahedron Lett., 2845 (1979).
7. IR and ^{1}H-NMR spectra were measured in CCl$_4$ solution unless otherwise stated. Representative characterization data includes: **6**, δ 1.06 (3H,s), 1.20 (3H,s), 1.47 (1H,d,J=12.5), 1.88 (1H,d,J=12.5), 1.6-2.7 (7H,m), 4.8-5.2 (2H,m), 5.4-6.0 (1H,m), ν 1725, *m/z* 190 (M$^+$); **15** (X=OH), δ 0.96 (3H,s), 1.27 (3H,s), 1.3-2.7 (10H,m), 4.06 (1H,s), 4.8-5.2 (2H,m), 5.4-6.0 (1H,m), ν 1710, *m/z* 208 (M$^+$); **16** (X=OH), δ 0.95 (3H,s), 1.02 (3H,s), 1.52 (1H,d,J=14), 1.78 (1H,d,J=14), 1.8-2.5 (7H,m), 3.10 (1H,br s), 3.2-3.5 (1H,m), 4.9-5.2 (2H,m), 5.4-6.0 (1H,m), ν 1740, *m/z* 208 (M$^+$); **23**, δ(CDCl$_3$) 0.99 (3H,s), 1.18 (3H,s), 1.72 (1H,d,J=13.5), 1.3-2.1 (8H,m), 2.12 (3H,s), 2.58 (2H,s), ν 1745, 1720, *m/z* 208 (M$^+$); **24**, δ(CDCl$_3$) 0.90 (3H,s), 1.21 (3H,s), 1.2-2.1 (7H,m), 1.78 (1H,d,J=13), 2.20 (2H,s), 2.41 (1H,br s), 5.67 (1H,s), ν 1710, 1645, *m/z* 190 (M$^+$); **25**, δ 0.88 (3H,s), 1.22 (3H,s), 1.3-2.1 (8H,m), 2.14 (1H,dd,J=9,4), 2.36 (1H,br s), 3.19 (3H,s), 3.28 (1H,dd,J=9.5,9), 3.45 (1H,dd,J=9.5,4), 5.55 (1H,s), ν 1705, 1645, *m/z* 234 (M$^+$); **5** δ(CDCl$_3$) 1.19 (3H,s), 1.23 (3H,s), 1.4-2.1 (10H,m), 2.48 (1H,dd,J=19.5,9.2), 2.67(1H,dd,J=19.5,12.2), 5.08 (1H,d,J=1.2), 5.88 (1H,d,J=1.2), ν 1725, 1640, *m/z* 204 (M$^+$).
8. Exclusive formation of **6** from **13** should be attributable to more electron-donating character of the ring olefin.
9. S.A. Monti, D.J. Bucheck, and J.C. Shepard, J. Org. Chem., **34**, 3080 (1969).
10. There have been many examples concerning C$_2$-C$_8$ bond cleavage of tricyclo[3.3.0.0^{2,8}]octan-3-one compounds. cf. K. Kon and S. Isoe, Tetrahedron Lett., **21**, 3399 (1980); P. Callant, H. De Wilde, and M. Vandewalle, Tetrahedron, **37**, 2079 (1981); M. Demuth and K. Schaffner, Angew. Chem. Int. Ed. Engl., **21**, 820 (1982) and references cited therein; K. Kon and S. Isoe, Helv. Chim. Acta, **66**, 755 (1983); K. Koyama and K. Kojima, Chem. Pharm. Bull., **32**, 2866 (1984); G. Mehta and D. Subrahmanyam, J. Chem. Soc., Chem. Commun., 768 (1985).
11. The Birch reduction (Run 1) is known to be mainly affected by stereo-electronic factor. cf. J.F. Ruppert and J.D. White, J. Am. Chem. Soc., **103**, 1808 (1981).
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