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A NEW SYNTHESIS OF dl-CORIOLIN A.
APPLICATION OF A NEW S_N2 REACTION AT A NEOPENTYLIC POSITION

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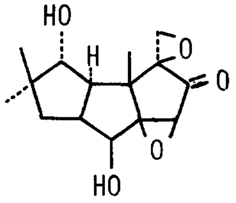
Abstract: Dicyclopentadiene has been stereoselectively converted to a key tricyclic intermediate for the total synthesis of coriolin, through a route which involves a new S_N2 reaction at a neopentylic position.

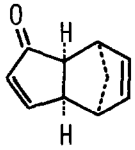
The highly oxygenated hirsutanoids, coriolins, isolated from Coriolus consors by H. Umezawa and coworkers[1a] has attracted attention, in particular because of the unusual antitumoric activity of coriolin B[1b]. A unique, synthetically attractive feature of coriolins is the multi-functionalized, cis,anti,cis-tricyclo[$6.3.0.0^{2,6}$]undecane skeleton with from seven to eight asymmetric centers and total syntheses of dl-coriolin A, a representative compound of this group, has recently been reported from four laboratories[2]. We should like to describe here a new synthesis of dl-coriolin A, starting from readily accessible dicyclopentadiene, through a route which involves a new S_N2 inversion reaction at a neopentylic position.

First, ketone 1[3], prepared from dicyclopentadiene, was converted to a dimethylated ketone 2 in 65% overall yield in three steps through $NaBH_4$ reduction[4], followed by Jones oxidation, and methylation ($^tBuOK/CH_3I/^tBuOH$-PhH/reflux). The reduction of the ketone 2 was effected stereoselectively by $LiAl(OCH_3)_3H$ (THF/0 °C/1 h) to give β-alcohol 3 as a single product (98%). Ozonization of 3 (MeOH/-78 °C) and subsequent decomposition of the ozonide with dimethyl sulfide yielded aldehyde 4, which was oxidized (Jones reagent/rt) to lactonic acid 5, mp 141-142 °C, in 76% yield from 3. Decarboxylation of 5 according to Kochi's method[5] afforded 6, mp 70-71 °C (84% based on the consumed 5, 46% conversion). The lactone 6 was then transformed into 7[6] in one pot by the sequence of treatments with (1) 5 equiv ^{t}AmONa/DMSO/rt/18 h, (2) 5 equiv H_2O/rt/6 h, and (3) excess CH_3I/rt/24 h, in almost quantitative yield.

For the purpose of synthesizing coriolins, it was essential to epimerize the β-oriented hydroxyl group of 7. Attempted hydride reduction ($LiAl(O^tBu)_3H$, AlH_3, DIBAL) of the ketone derived from 7 (Jones oxidation, 85%) to a diol 10, mp 80-81 °C, resulted in unsatisfactory stereoselectivity (yield 85%; 0, 66, 66%



Coriolin A



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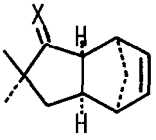
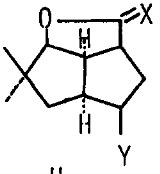


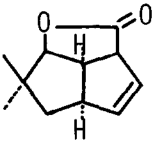
2 $X = O$

3 $X = \overset{OH}{\underset{H}{<}}$



4 $X = \overset{H}{\underset{OH}{<}}$, $Y = CHO$

5 $X = O$, $Y = CO_2H$



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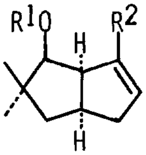
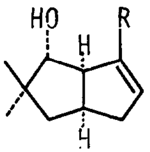


7 $R^1 = H$, $R^2 = CO_2CH_3$

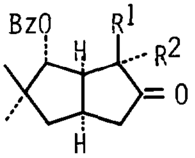
8 $R^1 = H$, $R^2 = CH_3$

9 $R^1 = SO_2CH_3$, $R^2 = CH_3$



10 $R = CH_2OH$

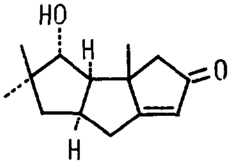
11 $R = CH_3$



12 $R^1 = CH_3$, $R^2 = H$

13 $R^1 = CH_3$, $R^2 = CH_2CHCl{=}CH_2$

14 $R^1 = CH_3$, $R^2 = CH_2COCH_3$



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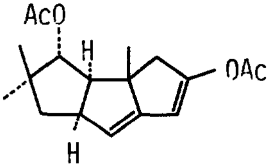

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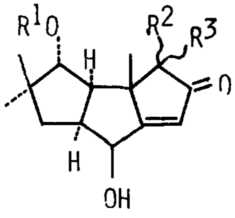
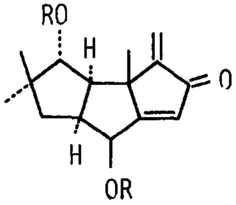


17 $R^1 = R^2 = R^3 = H$

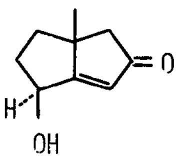
18 $R^1 = THP$, $R^2 = CH_3$, $R^3 = H$

19 $R^1 = THP$, $R^2 = CH_3$,
$R^3 = SePh$



20 $R = H$

21 $R = Ac$



22

inversion, respectively). Therefore the inversion of configuration through the S_N2 mechanism was undertaken. Although the extreme difficulty of the S_N2 reaction at a neopentylic position is well documented, it was felt that the reaction could be realized by using the powerful nucleophile superoxide[7]. Alcohol **8**, derived from **7** [(1) 3 equiv AlH_3/THF/0 °C/6 h (2) 1.2 equiv MsCl/1.2 equiv LiCl/1.2 equiv γ-collidine/DMF/0 °C/1 h (3) excess $LiAlH_4$/THF/rt/16 h], was mesylated (MsCl/Py) to give **9** in 80% overall yield from **7**. Reaction of **9** with KO_2 (5 quiv/5 equiv dibenzo-18-crown-6-ether/DMSO-DME/rt/48 h) followed by addition of excess water and $NaBH_4$ (10 equiv) gave the desired α-alcohol **11**[6,8], mp 52-53 °C, in 82% yield.

After benzoylation of **11**, the benzoate was converted to a ketone **12** via hydroboration-oxidation [(1) 3 equiv $BH_3\cdot$THF; H_2O_2, OH^- (2) Jones oxidation]. Chloropropenylation of **12** (1.2 equiv ^{t}BuOK/1.5 equiv 2,3-dichloropropene/^{t}BuOH-PhH/reflux) afforded **13**[6] in 54% yield from **11**. Treatment of **13** with mercuric acetate (1.2 equiv/HCO_2H/rt 15 min)[9] gave **14** in almost quantitative yield, and subsequent aldol condensation of **14** (5% methanolic KOH; elimination of methanol from the MeOH adduct of enone **15** by treatment with Al_2O_3) afforded a tricyclic enone **15**[6], mp 121-122 °C (60%). Stereoselective introduction of a hydroxyl group to the γ-position of the enone **15** was achieved through dienol acetate **16**[6,10], which in turn was derived from **15** (isopropenyl acetate/p-TsOH/reflux/24 h) in 90% yield (40% conversion). Oxidation of **16** (1.1 equiv of mCPBA/THF/0 °C/15 min), followed by basic hydrolysis ($NaHCO_3$/H_2O; 1N-LiOH), provided **17**[6] as a single product (75%). The configuration of the selectively formed hydroxyl group of **17** was shown to be β by comparison of its spectral data [δ 5.79 (1H, s, olefinic proton)] with those of the previously reported bicyclic coriolin model **22**[10] [δ 5.89 (1H, s), the α-hydroxy isomer of **22** shows a doublet peak with J= 1.7 Hz at δ 5.95]. α-Methylenation of **17** was carried out by the following procedure[11]. After pyranylation of **17**, the pyranyl ether was methylated (2.2 equiv LDA/excess CH_3I/-78 °C, 30 min→0 °C) to give **18**. Phenylselenylation of **18** (2.5 equiv LDA/3 equiv PhSeBr/-78 °C, 30 min→0 °C), followed by oxidation with 30% hydrogen peroxide, afforded a dienone **19**. Subsequently **19** was deprotected (AcOH-H_2O-THF) to give a diol **20**[6] in 65% yield from **17**. Both **20** and diacetate **21** derived from it showed ir and nmr spectral data identical with those reported in the literature[2a,2b].

Since the diol **20** was already transformed into dl-coriolin A[2a,2b], the above sequence of reactions means a new total synthesis of coriolin A starting from dicyclopentadiene.

References and Notes

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b. S. Danishefsky, R. Zamboni, M. Kahn, and S. J. Etheredge, *J. Am. Chem. Soc.*, **102**, 2097 (1980); S. Danishefsky, R. Zamboni, M. Kahn, and S. J. Etheredge, *J. Am. Chem. Soc.*, **103**, 3470 (1981).
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6) All new compounds in this paper gave satisfactory analytical and spectral data. Only perinent values are given in the following:
7: IR 3560, 1715, 1635 cm^{-1}; NMR δ 6.67 (1H, dd, J=4.2 Hz), 3.70 (1H, d, J=6 Hz), 3.69 (3H, s), **11**: IR 3440 cm^{-1}; NMR δ 5.10 (1H, m), 3.38 (1H, d, J=6 Hz), 1.78 (3H, d, J=1.5 Hz). **13**: IR 1740, 1720, 1633 cm^{-1}; NMR δ 5.20 (1H, d, J=1.5 Hz), 5.16 (1H, d, J=8 Hz), 2.61, 2.50 (ABq, J=15 Hz). **15**: IR 3480, 1710, 1640 cm^{-1}; NMR δ 5.68 (1H, d, J=1.5 Hz), 3.79 (1H, d, J=8 Hz). **16**: IR 1770, 1735, 1645, 1603, 1583 cm^{-1}; NMR δ 5.97 (1H, m), 5.09 (1H, d, J=4 Hz). 4.80 (1H, d, J=5 Hz), 2.12 (3H, s), 2.02 (3H, s). **17**: IR 3480, 1700, 1635 cm^{-1}; NMR δ 5.79 (1H, s), 4.61 (1H, d, J=5.5 Hz), 3.80 (1H, d, J=9 Hz). **20**: IR 3440, 1700, 1620 cm^{-1}; NMR δ 6.05 (1H, s), 5.94 (1H, s), 5.37 (1H, s), 4.68 (1H, d, J=6 Hz), 3.90 (1H, d, J=9 Hz), 1.52, 1.13, 0.94 (each 3H, s).

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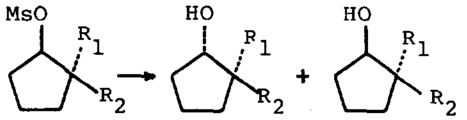
8) Under similar conditions a range of neopentyl mesylates undergoes the S$_N$2 reaction. Examples are shown in the following Figure.



23 **24**

	yield(%)	
	23	**24**
R_1=methyl, R_2=ethyl	45	12
R_1=methyl, R_2=allyl	72	24
R_1=ethyl, R_2=methyl	53	36
R_1=allyl, R_2=methyl	50	27

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