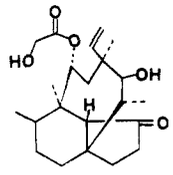
One-Step Synthesis of Tricyclo[5.2.2.0^{2,6}]undecane Derivatives: Precursors to Pleuromutilin

Summary: A versatile, one-step stereoselective synthesis of tricyclo[5.2.2.0^{2,6}]undecane derivatives and related compounds is used in a synthetic approach to the antibiotic pleuromutilin.

Sir: Pleuromutilin (1),[1,2] an antibiotic isolated from *Pleurotus mutilus*, is presently a synthetic objective in our laboratory. Our approach to this unusual diterpene is based on the premise that the tricyclic ring system and its accompanying stereochemistry can be successfully derived from a rigid, tetracyclic compound similar to **2**. This communication describes our successful route to **2** by using a remarkable one-step, stereoselective synthesis of the key intermediate **3**.



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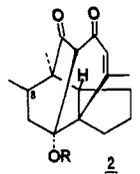

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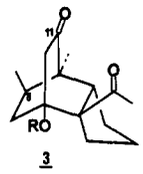

3

R = CH_2OCH_3

Given the difficulty of synthesizing tricyclo[5.2.2.0^{2,6}]-undecane derivatives such as **3** by current methods,[3] we are pleased to report that the reaction between the kinetic enolate of **4**[4,5] and 1-acetylcyclopentene (**5**)[6] proceeds in surprisingly good yield at −70 °C to give the endo adduct **3** as the sole product [mp 79–80 °C, 65–70% direct yield, 91% corrected yield; NMR ($CDCl_3$) δ 2.30 (3 H, s), 0.94 (3 H, s), 0.81 (3 H, d, J = 6.7 Hz); IR ($CHCl_3$) 1720, 1695 cm^{-1}][7,8] (Scheme I). The stereochemistry of the product was established by the transformation of **3** to the bridged, tetracyclic compound **2**, as illustrated in Scheme II.

Scheme I

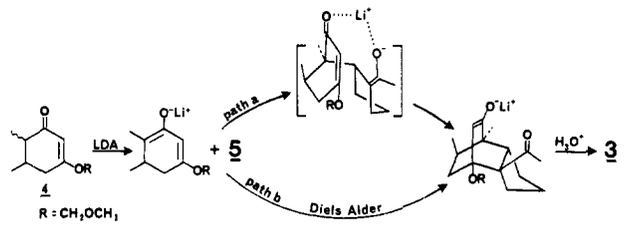

Table I

ENTRY	STARTING MATERIALS	PRODUCTS[a]	ISOLATED YIELD[b]	mp[c] (°C)	RXN CONDITIONS[d] (°C/hrs)
A	**4** (R = CH_2OCH_3), **5**	**3**	65–70% (91%)	79–80°	−70°/70 [e]
B[h]	**4**	**10**	28% (45%)	87–87.5°	−70°/100 [e]
C	**4**	**11**	51% (70%) exo:endo 8:1 −70°, 2:1 −30°, 1.5:1 −20°	exo: 95–96.5° endo: 98–99°	−30°/5 [f]
D	**12**	**5**	27% (31%)	147–148°	−70°/12 [f]
E	**12**		9% (9%)	65–66.5°	−70°/5 [f], −30°/6
F	(−)	**5**	68% (mixt) (81%) major:minor 2:1	minor: oil major: [i] 75.5–76.5°	−22°/4 [f]
G		**5**	32% (40%)	66–68°	−22°/4 [g]
H		**5**	10% (13%)	69.5–70°	−22°/3 [f]
I	**12**		33% (45%)	125–126°	−22°/4 [f]
J		**5**	13% (16%)	143–144°	−22°/5 [f]
K[j]	**5**	**5**	62% (72%)	55–56°	−70°/5 [f], −22°/2

[a] Endo assignment in entries D–J is based on entry A. [b] Yields in parentheses represent corrected yields (direct yield + additional yield from recovered starting material recycled once). [c] Uncorrected. [d] Times refer to duration of reaction at indicated temperature after addition of Michael acceptor to enolates at −70 °C; see footnote 8. All reactions warmed slowly (4–6 h) to room temperature before workup. Products in C–K isolated by TLC on silica gel. [e] See footnote 8. [f] LDA (1.2 equiv). Michael acceptor (1 equiv). [g] LDA (1.5 equiv), **5** (1.5 equiv). [h] See footnote 27. [i] $[\alpha]^{20}_D$ −46.4° (*c* 0.252 $CHCl_3$). [j] Assignment of stereochemistry is based on an examination of Dreiding models.

(1) Kavanagh, F.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 570. *Ibid.* **1952**, *38*, 555.

(2) Structure determination: Birch, A. J.; Cameron, O. W.; Holzapfel, C. W.; Rickards, R. W. *Chem. Ind. (London)* **1963**, 374. Birch, A. J.; Holzapfel, C. W.; Rickards, R. W. *Tetrahedron* **1966**, *22*, Suppl. 8, Part II, 359. Arigoni, D. *Gazz. Chim. Ital.* **1962**, *92*, 884. *Pure Appl. Chem.* **1968**, *17*, 331.

(3) A Diels–Alder reaction using 1,3-bis[(trimethylsilyl)oxy]-5-methylcyclohexa-1,3-diene and **5** was examined. Heating the mixture with C_6D_6 under vacuum in a sealed NMR tube at 200–240 °C over 6 days yielded no detectable amount of the desired adduct. Cf.: Ibuka, T.; Mori, Y.; Aoyama, T.; Inubushi, Y. *Chem. Pharm. Bull.* **1978**, *26*, 456.

(4) Cf.: Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *38*, 1775.

(5) Prepared in two steps from 5-methyl-1,3-cyclohexanedione (Crossley, A. W.; Renouf, N. *J. Chem. Soc., Trans.* **1915**, *107*, 602): (i) CH_3OCH_2Cl, KH, HMPA (1 equiv), DME, room temperature, 15 h [mp 56–57 °C, Et_2O, 66% (cf.: Coates, R. M.; Shaw, J. E. *J. Org. Chem.* **1970**, *35*, 2061)]; (ii) LDA (1.2 equiv), THF, −70 °C, 2 h; MeI (4 equiv), −70 °C, 2 h; warm to room temperature [**4**, oil, 91%, sufficiently pure for the next step (or 84% by distillation at 50–55 °C (0.0015 mm Hg))].

(6) Heilbron, I.; Jones, E. R. H.; Toogood, J. B.; Weedon, B. *J. Chem. Soc.* **1949**, 1827.

(7) Satisfactory combustion analyses and spectroscopic data were obtained for all compounds (with the exception of **7**, **8**, and **13** where the elemental composition was confirmed by high-resolution mass spectrometry).

(8) In a typical reaction, **4** (6 mmol) in dry THF (10 mL) was added dropwise with stirring to LDA (12.6 mmol) in THF (40 mL) under argon at −70 °C. After 1.5 h at −70 °C, **5** (9 mmol) in THF (10 mL) was added dropwise to the stirred, enolate solution. The mixture was maintained at −70 °C for 72 h by using a long, narrow flask stirred magnetically through a small Dewar, warmed slowly (6 h) to room temperature, and quenched with saturated aqueous NH_4Cl. The ethereal extract was successively washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to yield a crude oil. Unreacted **4** was removed by hydrolysis (20% aqueous 1:10 H_2SO_4–THF, 150 mL, 30 min, room temperature). The ethereal extract was washed with 5% aqueous NaOH, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), concentrated under high vacuum to remove residual **5**, and cooled overnight to produce a yellow crystalline solid (70%) (recrystallized from Et_2O–hexane, mp 79–80 °C).

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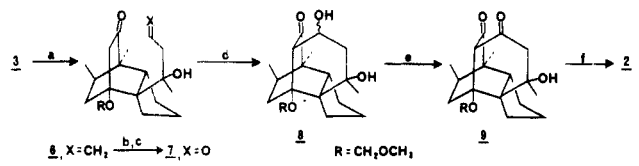
Scheme II[a]



(a) CH_2=$CHCH_2Li$ (2 equiv), THF, −78 °C, 1.5 h, 95%; (b) O_3, 1:1 MeOH-CH_2Cl_2, −78 °C; (c) $(MeO)_3P$, $NaHCO_3$, −78 °C to room temperature; (d) Et_2O/5% aqueous NaOH, two-phase/stirring, room temperature, 20 min; (e) PCC,[10] CH_2Cl_2, room temperature, 4 h; (f) Burgess' reagent,[11] benzene, reflux, 4 h.

Treatment of **3** with allyllithium[9] gave **6** as a single product (mp 93–94.5 °C). Ozonolysis, followed by reductive workup, converted **6** to the unstable aldehyde **7** (mp 108–111 °C), which under basic conditions cyclized to a mixture of diols **8** (oil) and in addition yielded **3** by a competing retroaldol process. Oxidation of the diol mixture afforded the crystalline hydroxy diketone **9** (mp 144–145 °C), which was smoothly dehydrated to the α,β-unsaturated diketone **2** [mp 121–122 °C; NMR ($CDCl_3$) δ 5.71 (1 H, br s), 3.34 (1 H, br s), 1.96 (3 H, d, J = 1.3 Hz), 1.01 (3 H, s), 0.90 (3 H, d, J = 6.9 Hz); IR ($CHCl_3$) 1725, 1675 cm^{-1}; UV (95% EtOH) λ_{max} 242 nm (ϵ 9000)]. We anticipated that the stereochemistry at C-8 in **3** (and consequently in **2**) would be defined by the path of least-hindered approach. Support for this assignment is based on the downfield shift (0.20 ppm) produced in the ^1H NMR δ value of the methyl group attached at C-8, on reduction ($NaBH_4$) of the carbonyl group at C-11.[12]

In order to test the scope of the reaction, a number of other systems were investigated and the results are summarized in Table I. Apart from entry A, yields have not been optimized. In many cases the product mixture contained significant amounts of recoverable starting materials, and hence the corrected yields are distinctly higher. Most of these systems have proved to be quite sensitive to reaction temperature. For entry A, higher temperatures yielded larger quantities of unreacted starting materials. This may reflect a higher rate of proton transfer competing with the addition. In other cases, particularly entries E, G, and H, higher temperatures led to increased quantities of side products. Although not thoroughly characterized, these additional products appear to be the result of single Michael additions. In one instance, entry C, the actual mode of addition was affected by the reaction temperature. As indicated in the table, 1-cyclopentenecarboxaldehyde (**11**) and the enolate of **4** underwent predominantly exo addition at −70 °C, but with increasing temperature the exo/endo ratio decreased to near unity at −20 °C.[13] Particular attention is drawn to entries E and F which represent attractive routes to spiro compounds and optically active intermediates, respectively. Furthermore, since methods already exist for the opening of bicyclo[2.2.2]-octane and bicyclo[2.2.1]heptane derivatives to substituted cyclohexane and cyclopentane rings,[14,15] the entries in Table I will provide a new route to substituted bicyclo-[4.3.0] and -[3.3.0] ring systems.

There are a number of reports which concern the dimerization of 2-cyclohexenones to crystalline solids under basic conditions.[16,17] While the structures of these related products were never satisfactorily elucidated, Ruzicka did propose structures which could have resulted from a sequential Michael addition. More recently, the analogous dimerization of 4,4-dimethylcyclopent-2-enone has been observed by Bellamy.[18] Other examples using simple Michael acceptors and the kinetic enolates of various substituted 2-cyclohexenones to produce bicyclo[2.2.2]-octanes have been published.[19–26] The stereochemistry of the major products, when determined, has been endo with only one exception.[21] Most of the authors have expressed a preference for the sequential Michael route (Scheme I, path a) over the anion-accelerated Diels–Alder mechanism (path b). Mildness of conditions and the presence of single Michael adducts among the products have been used to support the former mechanism.[19,26] A third possibility, an oxy-Claisen pathway, would not seem to be feasible here due to steric problems in the transition state, as judged from an examination of Dreiding models. At present there appears to be no good evidence for eliminating either mechanism, nor are there good reasons to believe that the same mechanism operates in all cases.

Considering the number of stereocenters which are defined in a single step from easily accessible starting materials, these reactions should prove to be very useful for various synthetic problems. We are currently investigating the application of these methods to the synthesis of other ring systems, as well as continuing our studies toward the total synthesis of pleuromutilin.

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(12) For an analogous assignment see: Cimarusti, C. M.; Wolinsky, J. *J. Org. Chem.* **1971**, *36*, 1871.
(13) Stereochemistry was determined by transformation of both adducts to their respective methyl ketones (MeLi (2.5 equiv), THF–Et_2O, −95 to −80 °C, 20 min; PCC, CH_2Cl_2, 1 h, room temperature; 60% overall). The aldehyde which was formed as the minor product at −70 °C yielded a methyl ketone identical with **3**.
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(27) **10** was synthesized from 3-methyl-2-cyclohexenol in three steps: (i) MeI (2 equiv), NaH (2 equiv), HMPA (1 equiv), THF, room temperature, 5 h; (ii) O_3, CH_2Cl_2, −78 °C; $(MeO)_3P$, −78 °C to room temperature; (iii) Et_2O/5% aqueous NaOH, stirring, room temperature, overnight; 45% overall.

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