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EFFICIENT STEREOSELECTIVE SYNTHESIS OF rel-(6S,7S,8S)-7-BUTYL-8-HYDROXY-1-AZASPIRO[5.5]UNDECAN-2-ONE, A KEY INTERMEDIATE FOR PERHYDROHISTRIONICOTOXIN, AND ITS rel-(6R) ISOMER

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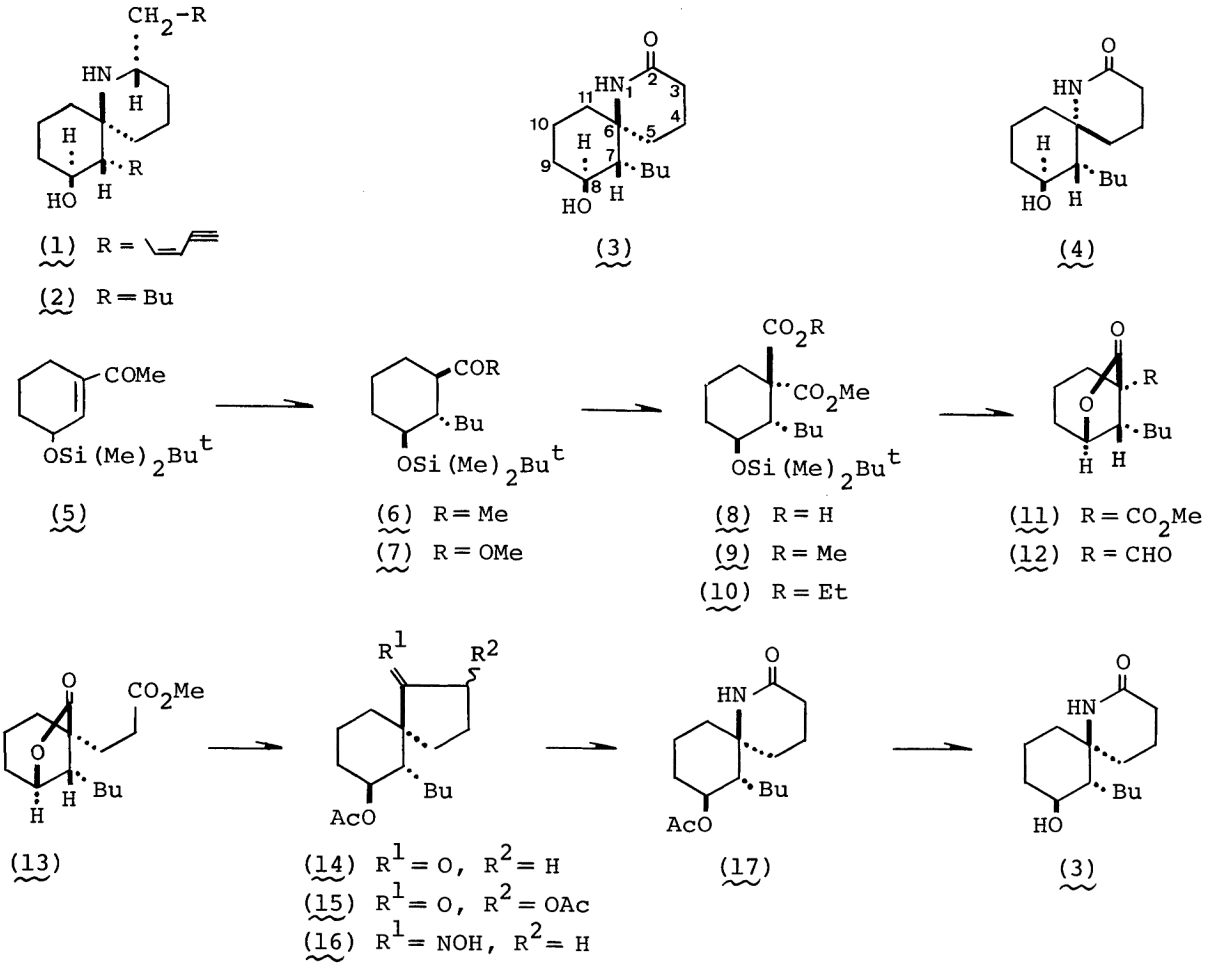
Using 3-t-butyldimethylsilyloxy-1-cyclohexenyl methyl ketone as a starting material, a simple stereoselective synthesis of rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one, a useful intermediate for the synthesis of pharmacologically important alkaloid perhydrohistrionicotoxin, and its rel-(6R) isomer, was described.

Histrionicotoxin (1), a spiropiperidine alkaloid isolated from the Columbian frog Dendrobates histrionicus, and its perhydro derivative (2) possess unique biological activities such as cholinolytics and modifiers of ionic channels in nerves, and the toxins have been reported to be samples of great promise for pharmacological studies.[1] It has also been reported that simple 1-azaspiro[5.5]-undecane derivatives possess analgetic, antipyretic, and antiphlogistic activity.[2] The scarcity of natural histrionicotoxins and unusual spiropiperidine structure of the bases have urged chemists to develop an efficient synthetic method for the alkaloids.[3] For pharmacological studies on the structure-activity relationship, we have developed an efficient stereoselective synthetic route to rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (3), a key intermediate for the perhydrohistrionicotoxin synthesis, and its (6R) isomer (4), and we describe herein our results in this area.

1) Synthesis of rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (3)[4]

The butylated ketone (6) obtained by the 1,4-addition reaction of the enone (5) with a new reagent $BuCu \cdot AlCl_3$,[5] was converted to the ester (7) in 96% overall yield by four successive operations [1). lithium diisopropylamide (LDA), -70∿-40°C; 2). TMSCl-Et_3N, -70∿-10°C; 3). O_3, -70°C; 4). diazomethane]. Treatment of 7 with LDA in THF, followed by carboxylation with CO_2 afforded the rather labile acid (8). The acid (8) was allowed to react with diazomethane and diazoethane to give the diesters (9, 95%) and (10, 80%), respectively. The stereochemistry of the carboxyl group in 8 was assigned based on the fact that dil HCl treatment at 50°C of both the esters (9 and 10) yielded the same lactone (11)[IR($CHCl_3$), 1775 and 1734 cm^{-1}] in high yields. Reaction of 11 with diisobutylaluminum hydride in a mixture of toluene and hexane (1:4) at -70°C, followed by oxidation with pyridinium chlorochromate[6] gave the labile aldehyde (12) in 42% yield. Treatment of 12 with



$(MeO)_2(O)P{=}CHCO_2Me$ in a mixture of benzene and Et_2O (1:1) at 0°C, followed by catalytic hydrogenation over PtO_2, afforded the lactone-ester (13) [IR($CHCl_3$), 1763 and 1732 cm^{-1}] in 74% yield.

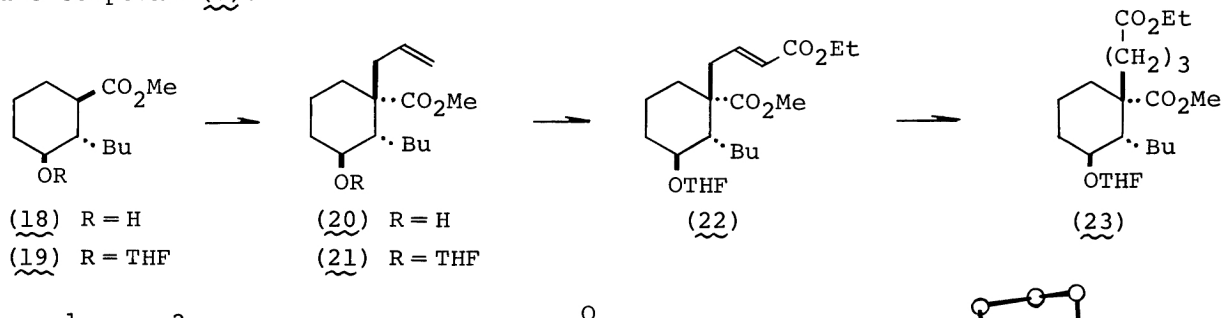
With the lactone-ester (13) in hand, the next task was the spirocyclization. The acyloin condensation[7] was effectively employed for the present purpose. Thus, treatment of 13 with sodium in the presence of TMSCl in boiling toluene, followed by successive treatments with 5% HCl at 0°C for 15 min and then Ac_2O-pyridine-4-dimethylaminopyridine (50:50:1) in $CHCl_3$ gave the spiranes (14, 16% yield) and (15, 44% yield). The acetoxyketone (15) was readily reduced with Zn-AcOH to yield the compound (14) in acceptable yield. The acetoxy-oxime (16), obtained by a conventional method from 14, was treated with p-TsCl-pyridine to afford the 1-aza-spirane (17) (mp 153∿154°C; IR($CHCl_3$); 3350(NH), 1724(acetate), and 1645 cm^{-1} (lactam); 33% yield), which on hydrolysis with NaOMe in MeOH gave rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (3) in 81% yield. The synthesized compound (3) was identified with an authentic sample kindly provided by Professor Evans.[8] Our synthesis of 3 constitutes a new stereoselective synthesis of perhydrohistrionicotoxin (2), since 3 has been converted to perhydrohistrionicotoxin (2) by Kishi,[3e] Corey,[3b] and Evans.[3f,8]

2) Synthesis of rel-(6R,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (4)

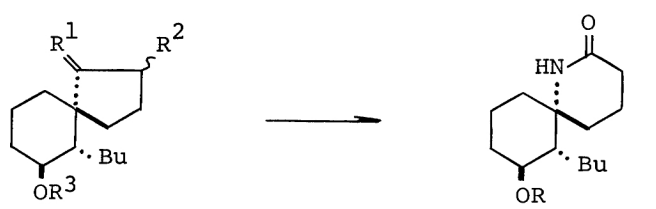
For the purpose of pharmacological studies on structure-activity relationship, the rel-(6R) isomer (4) of 3 was stereoselectively synthesized by the following reaction sequences.

The hydroxy-ester (18), obtained by acidic hydrolysis of 7, was treated with 2,3-dihydrofuran in the presence of a catalytic amount of pyridinium p-toluenesulfonate[9] to yield the ester (19) in 95% yield. Treatment of 19 with $KN(TMS)_2$ in THF at room temperature for 1 h and the resulting anion was alkylated with allyl bromide, and then treated with 5% HCl to yield the alkylated product (20) in 65% yield after silica gel column chromatography.[10] The tetrahydrofuranyl ether (21), prepared from 20 in 92% yield, was allowed to react with OsO_4-$NaIO_4$-N-methylmorpholine-1-oxide[11] in aqueous THF and the resulting aldehyde was subjected to the Wadsworth-Emmons reaction with $(EtO)_2(O)P{=}CHCO_2Et$ affording the enoate (22) in 76% overall yield. The diester (23), resulted from 22 by catalytic hydrogenation over PtO_2 in 98% yield, was subjected to the Dieckmann reaction with KH[12] to yield the spirane (24) in 87% yield. Decarboxylation of 24 with DMSO-H_2O-LiCl-$NaHCO_3$ (300:100:2:1) at 150°C (bath temp) gave the ketone (25) in 92% yield, which on heating with $NH_2OH\cdot HCl$-NaOAc in aqueous MeOH in a sealed tube at 170°C for 36 h afforded the oxime (26) (mp 56°C) in 87% yield. The Beckmann rearrangement of 26 with p-TsCl-pyridine gave the lactamtosylate (27) (mp 164~165°C, 38% yield), and a single crystal X-ray analysis of 27 provided convincing evidence for the structure (27). Finally, removal of p-toluenesulfonyl group in 27 was successfully achieved by using sodium-naphthalene in dry THF at room temperature to yield rel-(6R,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (4).

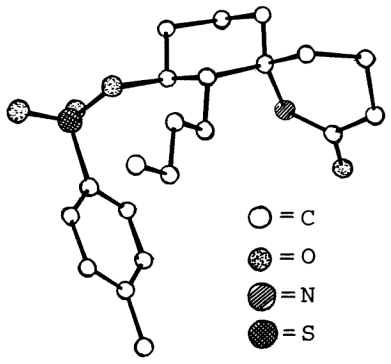
Thus, we have synthesized rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]-undecan-2-one (3), a key intermediate for the synthesis of perhydrohistrionicotoxin (2), and its rel-(6R) isomer in a stereoselective manner starting from the same compound (5).



(18) R = H
(19) R = THF
(20) R = H
(21) R = THF
(22)
(23)



(24) R^1 = O, R^2 = CO_2Et, R^3 = THF
(25) R^1 = O, R^2 = H, R^3 = THF
(26) R^1 = NOH, R^2 = R^3 = H
(27) R = Ts
(4) R = H



Stereoview of 27

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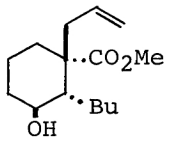

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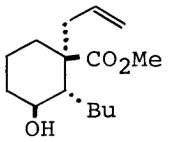

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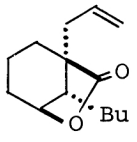

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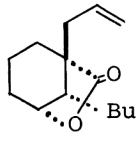

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