AN APPROACH TO THE SKELETON OF RAUWOLFIA ALKALOIDS: A GENERAL SYNTHESIS OF 3,8-EPOXY-7-KETO-6-OXABICYCLO[3.2.1]OCTANE DERIVATIVES

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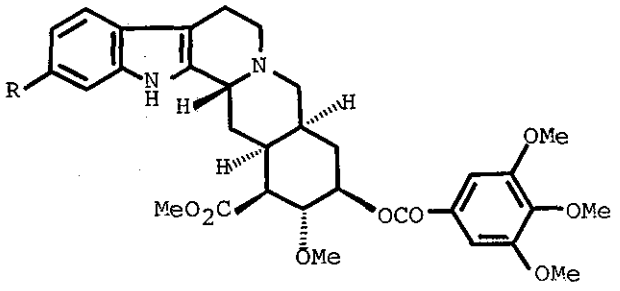
Halolactonization of the Diels-Alder adduct (3a) derived from bis(trimethylsilyl)allene dicarboxylate (2) and furan, followed by a treatment of the products (5a) and (5c) with diazomethane, afforded the corresponding α,β-unsaturated methyl esters (5b) and (5d), respectively. Catalytic hydrogenation of both compounds provided the desired methyl esters (4a) and (4b) which were identical with the compounds derived from Arndt-Eistert reaction of the halolactonic acids (7a) and (7c), respectively.

In our studies toward a total synthesis of the Rauwolfia

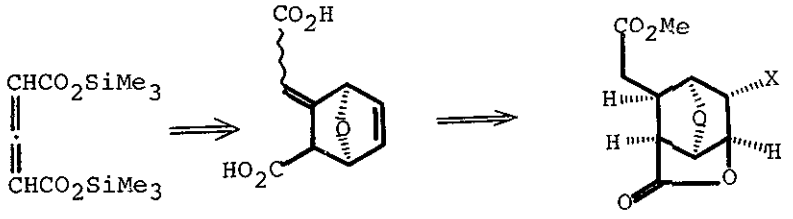
alkaloids, deserpidine (1a), reserpine (1b) and their analogues, a synthesis of the lactonic esters (4a and 4b) was essential for the construction of the nontryptamine part of these alkaloids.

On these requirement we have examined a cycloaddition reaction of bis(trimethylsilyl)allene dicarboxylate (2)[1] with furan[2] and a conversion of the cycloadduct (3a) into the 3,8-epoxy-7-keto-6-oxabicyclo[3.2.1]octane derivatives (4a and 4b) which would be important intermediates for deserpidine (1a) and reserpine (1b). Here we wish to report our successful results.

Chart 1



1a R:H
1b R:OMe

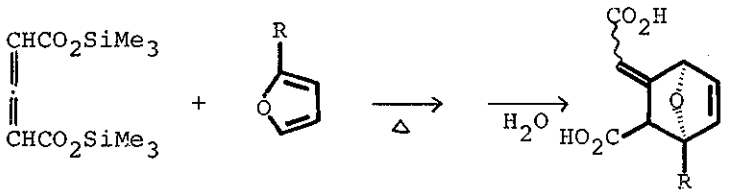


2 3

4a : X=I
4b : X=Br

The reaction of the allene dicarboxylate (2) with several homocyclic dienes are summarised in the following Table. All of these reactions were carried out in dry benzene solution and sealed tube. These cycloadducts were also characterized as the corresponding dimethyl ethers by treatment with an excess of diazomethane.

Table Reaction of the allene with furan derivatives



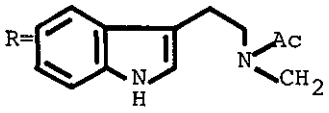
2 3

Diene	Reaction conditions Temp.(°C)	Time (h)	Product[3]	Yield (%)[4]
Furan	110	3.5	3a	88
Benzyl furfuryl ether	110	3	3b	8.1
	50	3	3b	40.4
Furfuryl alcohol	45	24	3c	23.4
N-Acetyl-N-furfuryl-tryptamine	110	12	3d	41.5

3a : R=H

3b : R=CH_2OCH_2Ph

3c : R=CH_2OH

3d : R= 

We can develop a synthetic method of the key material (3a) by a cycloaddition reaction and, therefore, a conversion of this compound into the lactonic esters (4a and 4b) was examined as follows.

Thus, halolactonization[5] of the cycloadducts (3a) (0.5 N $NaHCO_3$ solution, I_2, KI, room temperature, 2.5 hr) afforded the iodolactonic acid (5a), mp 125 - 126° (decomp.), ir (KBr) 1775 and 1695 cm^{-1}, in 53 % yield, which was treated with an excess of diazomethane to give the corresponding methyl ester (5b), in almost quantitative yield, ir ($CHCl_3$) 1795 and 1715 cm^{-1}; δ 3.86 (3H, s), 4.05 (1H, s), 4.18 (1H, dd, J = 4 and 2 Hz), 5.08 (1H, s), 5.25 (1H, d, J = 4 Hz), 5.56 (1H, t, J = 4 Hz), 6.18 (1H, d, J = 2 Hz).

Catalytic hydrogenation of this α,β-unsaturated methyl ester in methanol over Adams catalyst provided the desired methyl ester (4a), mp 131 ∿ 134°(decomp.), ir ($CHCl_3$) 1770 and 1725 cm^{-1}; δ 2.47 (2H, m), 2.77 (2H, m), 3.63 (3H, s), 3.99 (1H, s), after purification with preparative thick layer chromatography (50 % ethyl acetate-hexane).

The correct stereochemistry of this lactonic ester (4a) was proved by the comparison with the authentic sample derived from the lactonic acid (7a) by Arndt-Eistert reaction.

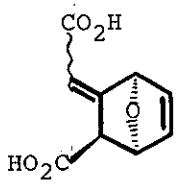
Thus, the iodolactonization of the known Diels-Alder adduct (6)[6] afforded, in 38.3 % yield, the iodolactonic acid (7a), mp 185 ∿ 187°, ir (KBr) 1770 and 1720 cm^{-1}; δ 2.93 (1H, dd, J = 10 and 5 Hz), 3.23 (1H, dd, J = 10 and 4 Hz), 4.63 (1H, s), 4.83 (1H, d, J = 4 Hz), 5.12 (1H, d, J = 5 Hz), 5.40 (1H, t, J = 5 Hz). This lactone was also characterized as the corresponding methyl ester (7b), mp

167 ∿ 169°, ir (KBr) 1785 and 1730 cm^{-1}; δ 2.94 (1H, dd, J = 9 and 5 Hz), 3.25 (1H, dd, J = 9 and 4 Hz), 3.70 (3H, s), 4.63 (1H, s), 4.86 (1H, d, J = 4 Hz), 5.15 (1H, d, J = 5 Hz), 5.44 (1H, t, J = 5 Hz). The reaction[7] of the lactonic acid (7a) with oxalyl chloride in refluxing dry benzene gave the acid chloride (8a), which was treated with an excess of diazomethane in ether to provide the diazoketone (8b), mp 147 ∿ 149°, ir (KBr) 2150 and 1790 cm^{-1}. This compound was refluxed for 1 hr in absolute methanol in the presence of freshly prepared silver oxide to give the desired methyl ester (4a) after purification on silica gel chromatography. The tlc behaviour, ir and nmr spectra of this ester were identical with those of the compound (4a) derived from the another route.

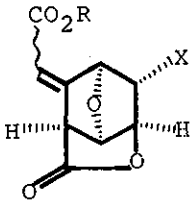
The bromolactonic ester (4b) was also made by both methods described above. Namely, bromolactonization of the dicarboxylic acid (3a) (0.8 N NaOH solution, $NaHCO_3$, Br_2, room temperature, 2 hr), followed by a treatment of the crude bromolactonic acid (5c) with an excess of diazomethane gave, in 34 % yield, the pure methyl ester (5d), ir ($CHCl_3$) 1795 and 1720 cm^{-1}; δ 3.90 (3H, s), 3.94 (1H, s), 4.15 (1H, dd, J = 2 and 5 Hz), 4.99 (1H, s), 5.00 (1H, d, J = 5 Hz), 5.53 (1H, t, J = 5 Hz), 6.10 (1H, d, J = 2 Hz), after purification on silica gel chromatography.

Hydrogenation of this ester over Adams catalyst in methanol afforded the crude product, which was separated by preparative thick layer chromatography (5 % methanol-chloroform) to give, in 72.3 % yield, the pure methyl ester (4b), mp 135 ∿ 138°, ir ($CHCl_3$) 1780 and1725 cm^{-1}, δ 2.47 (2H, m), 2.75 (2H, m), 3.70 (3H, s), 4.03 (1H, s), 4.71 (1H, br), 4.93 (1H, d, J = 5 Hz), 5.37 (1H, t, J = 5 Hz).

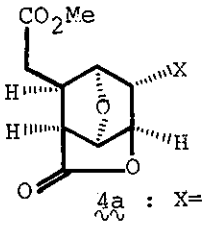
Chart 2



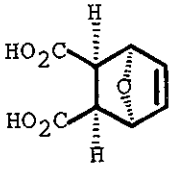
3a



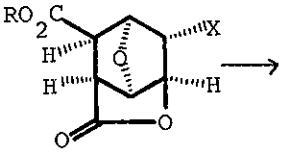
5a : R=H, X=I
5b : R=Me, X=I
5c : R=H, X=Br
5d : R=Me, X=Br



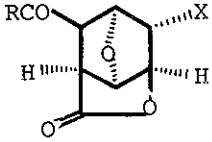
4a : X=I
4b : X=Br



6



7a : X=I, R=H
7b : X=I, R=Me
7c : X=Br, R=H

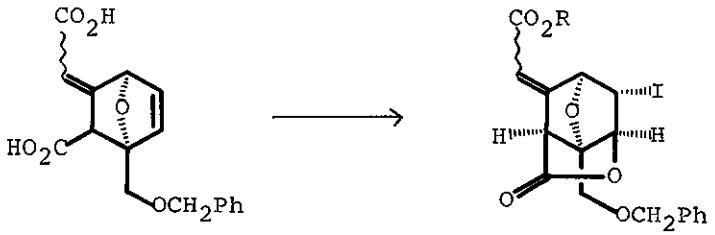


8a : X=I, R=Cl
8b : X=I, R=CHN_2
8c : X=Br, R=Cl
8d : X=Br, R=CHN_2

This lactonic ester was completely identical with the compound (4b) in tlc behaviour, ir and nmr spectral comparisons, the latter of which was synthesised via the acid chloride (8c) and the diazoketone (8d) from the known bromolactonic acid (7c)[6] in 47.4 % yield.

Furthermore, the halolactonization of the dicarboxylic acid (3b) was also examined. Halolactonization of the dicarboxylic acid (3b) (0.5 N $NaHCO_3$ solution, I_2, KI, room temperature, 3 hr) gave, in 93.5 % yield, the iodolactonic acid (9a), mp 134 ∿ 136°, ir (KBr) 1800 and 1700 cm^{-1}, which was also characterized as the corresponding methyl ester (9b), ir ($CHCl_3$) 1800 and 1720 cm^{-1}; δ 3.77 (3H, s), 3.97 (2H, s), 4.00 (1H, s), 4.63 (2H, s), 4.97 (1H, s), 5.00 (1H, s), 6.05 (1H, d, J = 2 Hz)[8], 7.27 (5H, s).

Chart 3



3b

9a : R=H
9b : R=Me

Thus, we could provide a simple and general method for the synthesis of 3,8-epoxy-7-keto-6-oxabicyclo[3.2.1]octane derivatives as the key intermediate for the synthesis of Rauwolfia alkaloids.

A total synthesis of deserpidine (1a), reserpine (1b) and the other indole alkaloids according to this method is in progress in our laboratory.

REFERENCES

1. This compound, bp 84° (0.03 mmHg), (colourless oil) was prepared from allene dicarboxylic acid, trimethylchlorosilane and hexamethyldisilazane.
2. P. Kurtz, H. Gold, and H. Disselnkötter, Annalen, 1959, 624. 1; M. Bertrand and J. Legras, Bull. Soc. chim. France, 1967, 4336; G. Büchi and J. A. Carlson, J. Amer. Chem. Soc., 1968, 90, 5336; A. P. Kozikowski, W. C. Floyd, and M. P. Kuniak, J. C. S. Chem. Comm., 1977, 582.
3. The cycloadducts (3) are a mixture of geometric isomer of double bond. The regiochemistry of the cycloadducts was determined by decoupling procedure of 100 MHz nmr spectrometry. The cycloadduct 3a derived from furan and 2 shows the methine proton adjacent to the carboxyl group at 3.97 as double doublet having J = 5 and 2 Hz in its nmr spectrum. The proton at the same position in the cycloadducts (3b and 3c) resonates at 3.95, and 4.20 as a doublet (J = 2 Hz), thus ruling out an another possible structure due to regioselectivity of cycloaddition reaction.
4. The yield of these cycloadducts was calculated as the corresponding dicarboxylic acids after hydrolysis with water.
5. H. O. House, Modern Synthetic Reactions, W. A. Benjamin, Inc. Menlo Park, California, 1972, p. 441 and references cited

therein.

6. J. A. Berson and R. Swidler, J. Amer. Chem. Soc., 1953, 75, 1721 and references cited therein.

7. W. E. Backmann and W. S. Struve, Org. Reactions, 1942, 1, 38.

8. The counterpart of this proton can not be assigned by overlapping with the protons resonated in upfield.

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