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SYNTHESIS OF MACROCYCLIC LACTONES APPLYING INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION : SYNTHESIS OF (±)-A26771B

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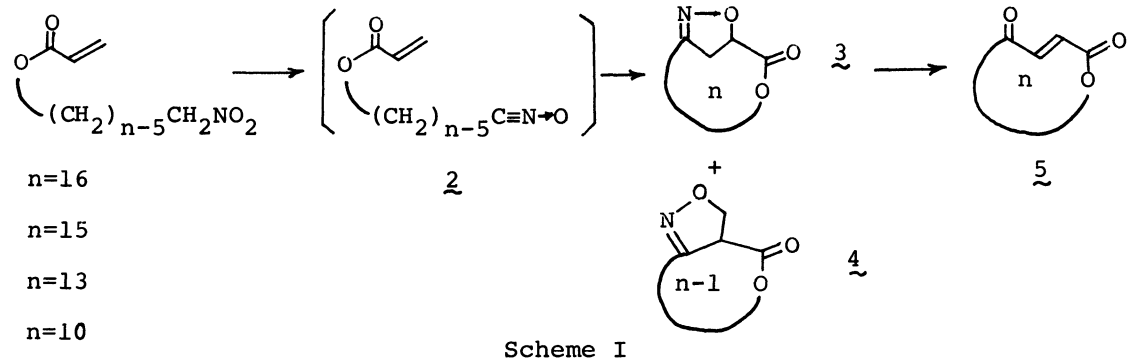
The intramolecular 1,3-dipolar cycloaddition of the nitrile oxides derived from ω-nitroalkyl acrylates gave isoxazoline fused macrocyclic lactones. The direction of 1,3-dipolar cycloaddition is strongly affected by the ring size of forming lactones. Utilizing this method, total synthesis of (±)-A26771B was achieved.

In our project[1-3] for the total synthesis of γ-oxygenated-α,β-unsaturated lactone system[4], we have shown that 16-membered dilactone was obtained in 85% yield by the double 1,3-dipolar cycloaddition of the silyl nitronate drived from 1-methyl-4-nitrobutyl acrylate.[3] The product was easily transformed into (±)-pyrenophorin. We have examined the possibility of the formation of macrocyclic monolactones by the intramolecular 1,3-dipolar cycloaddition of silyl nitronates or nitrile oxides. The process would be especially useful when the desired system is a γ-oxygenated-α,β-unsaturated lactone, since this should be obtained easily from the primary product, isoxazoline derivative.[3,5]



1a n=16
1b n=15
1c n=13
1d n=10

Scheme I

First, the intramolecular 1,3-dipolar cycloaddition of 1a[6] via its silyl nitronate was examined. Treatment of 1a (1 mmol) with 10 molar amounts of chlorotrimethylsilane and triethylamine in dry benzene (300 ml) at 30-35°C for 7 days, revealed the poor reactivity of silyl nitronate and gave the desired lactone (3a) in only 19% yield after acid treatment (run 1). When p-chlorophenyl isocyanate was used instead of chlorotrimethylsilane to carry out the intramolecular 1,3-dipolar cycloaddition via the nitrile oxide (2a), the reaction proceeded relatively fast and gave 3a in 51% yield under the similar reaction conditions (run 2). Under the longer reaction period (14 days), 3a was obtained in the higher (57%) yield (run 3). To avoid the long reaction period, the reaction was carried out in refluxing benzene and the effect of reaction time was examined (run 4-7). Due to the slow

decomposition of 3a under the conditions, the yield of 3a reached maximum (67%) at about 20 h and then gradually dropped. Similar reactions of 1b and 1c gave the anticipated lactones (3b and 3c) in 64 and 68% yields along with small amount of unexpected lactones (4b and 4c) which were formed by reverse directed 1,3-dipolar cycloaddition[7] (run 8 and 9). In the case of 1d, only the 9-membered lactone (4d) was obtained (run 10). It is worthy to note that, in contrast with the fact that intermolecular 1,3-dipolar cycloaddition of nitrile oxides with acrylic esters gives exclusively 5-alkoxycarbonyl isoxazoline derivatives, the direction of intramolecular 1,3-dipolar cycloaddition is strongly affected by the ring size of forming lactones.

Table Intramolecular 1,3-Dipolar Cycloaddition of 1a-d

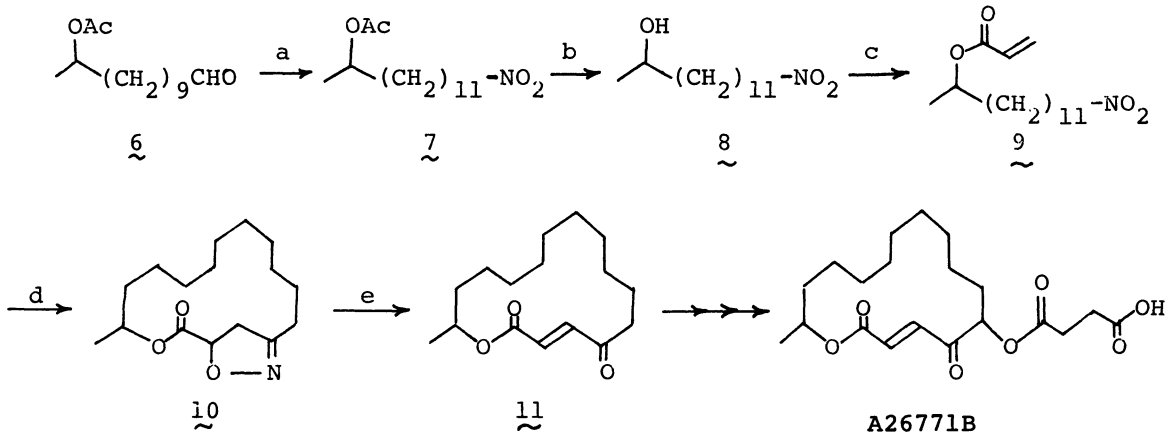
Run	n	Reagents[a]	Temp °C	time	Yield(%) 3[b]	Yield(%) 4[b]
1	16	A	30-35	7 days	<19	-
2	16	B	30-35	7 days	51	-
3	16	B	30-35	14 days	57	-
4	16	B	80	12 h	51	-
5	16	B	80	20 h	67	-
6	16	B	80	24 h	60	-
7	16	B	80	30 h	52	-
8	15	B	80	18 h	64	10
9	13	B	80	18 h	68	14
10	10	B	80	18 h	-	44

a) Ten molar amounts of reagents were used; A:Me_3SiCl-Et_3N, B:p-ClC_6H_4NCO-Et_3N.
b) All of these compounds were confirmed by ir, nmr, and mass spectral data and elemental analyses.[8]

Typical procedure: The dry benzene solution (300 ml) of 1b (1 mmol), p-chlorophenyl isocyanate (10 mmol), and triethylamine (10 mmol) was refluxed under argon atmosphere for 18 h. After cooling to room temperature, methanol (5 ml) was added and the volatile compounds were removed under reduced pressure. Methyl N-(p-chlorophenyl)carbamate and N,N'-bis(p-chlorophenyl)urea were removed by column chromatography. The crude material which contained a small amount of p-chloroaniline was treated with a small amount of acetic anhydride and pure 3b and 4b were isolated in 64 and 10% yield by subsequent preparative tlc (Silica gel: hexane-ether 1:1).

Finally, this method was applied to the synthesis of (±)-A26771B[9] (Schem II).

The nitro compound 7 was prepared in 58% yield by the method of Wollenberg and Miller[10] from the aldehyde 6[2]. Basic hydrolysis followed by acylation with acryloyl chloride[3] gave 9 in 81% yield from 7. Cyclization of 9 at 60-65°C for 36 h afforded 10[11] in 50% yield. Hydrogenation under acidic conditions followed by dehydration[3] afforded 11 in 73% yield. The structure was confirmed by direct comparison with authentic sample[2]. The lactone 11 is easily converted to (±)-A26771B[2].



Reagents: a) CH_3NO_2/KF, Ac_2O, $NaBH_4$; b) NaOH; c) $CH_2=CH_2COCl/PhNMe_2$; d) $P\text{-}ClC_6H_4NC{=}O/Et_3N$; e) $Pd\text{-}C/H_2$, $(CF_3CO)_2O\text{-}Et_3N$

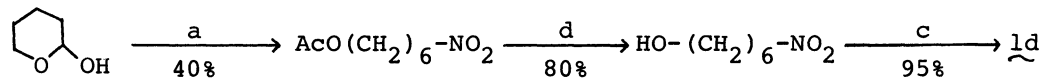
Scheme II

References

1) M. Asaoka, N. Yanagida, N. Sugimura, and H. Takei, Bull. Chem. Soc. Jpn., 53, 1061 (1980).
2) M. Asaoka, N. Yanagida, and H. Takei, Tetrahedron Lett., 21, 4611 (1980).
3) M. Asaoka, T. Mukuta, and H. Takei, ibid., 22, 735 (1981).
4) For reviews see K. C. Nicolau, Tetrahedron, 33, 683 (1977); S. Masamune, Gordon S. Bates, and J. W. Corcoran, Angew. Chem. Int. Ed. Engl. 16, 585-607 (1977).
5) a) K. Torssell and O. Zeuthen, Acta Chem. Scand., B 32, 118 (1978); b) S. C. Sharma and K. Torssell, ibid., B 33, 379 (1979).
6) The ω-nitroalkyl acrylates (1a-d) were prerared as follows.

$$CH_2=CH(CH_2)_8\text{-}CHO \xrightarrow[57\%]{a} CH_2=CH(CH_2)_{10}\text{-}NO_2 \xrightarrow[69\%]{b} HO\text{-}(CH_2)_{12}\text{-}NO_2 \xrightarrow[76\%]{c} 1a$$

$$AcO\text{-}(CH_2)_m\text{-}CHO \xrightarrow[\substack{m=9\ 67\% \\ m=7\ 69\%}]{a} AcO(CH_2)_{m+2}\text{-}NO_2 \xrightarrow[\substack{m=9\ 98\% \\ m=7\ 97\%}]{d} HO\text{-}(CH_2)_{m+2}\text{-}NO_2 \xrightarrow[\substack{m=9\ 84\% \\ m=7\ 93\%}]{c} 1b,\ 1c$$



a) CH_3NO_2/KF, Ac_2O, $NaBH_4$; b) B_2H_6, H_2O_2; c) $CH_2=CHCOCl/PhNMe_2$; d) NaOH

7) L. Garanti, A. Sala, and G. Zecchi, J. Org. Chem., 40, 2403 (1975).
8) The melting points and the nmr spectral data are shown below. 3a; mp47-48°C, nmr($CDCl_3$):δ=1.30(18H, s), 2.20-2.72(2H, m), 3.23(2H, d), 4.00-4.52(2H, m), 5.02(1H, dd), 3b; mp 64-66°c, nmr($CDCl_3$):δ=1.32(14H, s), 1.65(2H, brs), 2.23-2.67(2H, m), 3.25(2H, d), 4.10-4.38(2H, m), 5.00(1H, t), 3c; mp 47.5-48.5°c, nmr($CDCl_3$):δ=1.35(12H, brs), 2.23-2.67(2H, m), 3.22(2H, d), 3.80-4.62(2H, m), 5.00(1H, dd), 4b; mp 51.5-52.5°c, nmr($CDCl_3$):δ=1.36(16H, brs), 2.12-2.60(2H, brd), 3.80-4.70(5H, m), 4c; oil, nmr($CDCl_3$):δ=1.05-2.10(12H, m), 2.27-2.68(2H, m), 3.90-4.74(5H, m), 4d; mp 82-83°c, nmr($CDCl_3$):δ=1.10-2.10(6H, m), 2.47-2.90(2H, m), 3.73-5.00(5H, m)
9) a) Isolation: K. H. Michel, P. V. Demarco, and R. Nagarajan, J. Antibiot., 30,

571 (1977).
b) Synthesis of (-)-A26771B: K. Tatsuta, A. Nakagawa, S. Maniwa, and M. Kinoshita, Tetrahedron Lett., 21, 1479 (1980), K. Tatsuta, A. Nakagawa, S. Maniwa, and M. Kinoshita, Nippon Kagaku Kaishi, 1981, 762.
c) Synthesis of (±)-A26771B methyl ester: T. H. Hase and E. Nylung, Tetrahedron Lett., 1979, 2633.
d) Synthesis of (±)-A26771B: reference 2.
10) R. H. Wollenberg and S. J. Miller, Tetrahedron Lett., 1978, 3219.
11) Two diastereomeric isomers (10a and 10b) were isolated by tlc in 39% and 11% yields. Though the stereochmistry could not be elucidated, both were confirmed by ir, nmr, and mass spectral data and elemental analyses. The nmr spectral data and the melting points are shown below. 10a; mp 98.5-99.5°c, nmr($CDCl_3$): δ=1.22(3H, d), 1.28(18H, s), 2.20-2.73(2H, m), 3.19(2H, d), 4.98(1H, dd), 4.77-5.23(1H, m), 10b; mp 101.5-103.5°c, nmr($CDCl_3$);δ=1.23(3H, d), 1.27(18H, s), 2.16-2.60(2H, m), 3.18(2H, d), 4.95(1H, dd), 4.68-5.14(1H, m).

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