CHEMISTRY LETTERS, pp. 893-894, 1989. 

# Convenient Synthesis of Disubstituted Cyclic Ethers. Syntheses of (-)-cis-Rose Oxide and (cis-6-Methyltetrahydropyran-2-yl)acetic Acid

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Disubstituted cyclic ethers are stereoselectively prepared on the successive treatment of δ- or ε-lactones with t-butyldimethylsiloxy-1-ethoxyethene and silyl nucleophiles in the presence of a catalytic amount of trityl hexachloroantimonate or a catalyst system of antimony pentachloride, chlorotrimethylsilane and tin(II) iodide. The present procedure is effectively applied to short syntheses of (-)-cis-rose oxide and (cis-6-methyltetrahydropyran-2-yl)acetic acid, a constituent of civet.

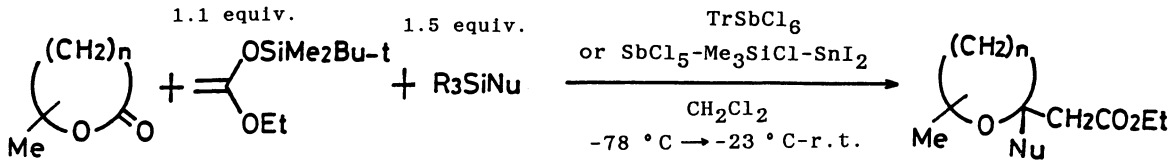
In the previous paper,[1] we have reported that 2-ethoxycarbonylmethyl substituted cyclic ethers are prepared from lactones on treatment with t-butyldimethylsiloxy-1-ethoxyethene and silyl nucleophiles (triethylsilane, allyltrimethylsilane, trimethylsilyl cyanide etc.) by promotion of trityl salts such as $TrSbCl_6$, $TrSbF_6$, $TrClO_4$ or by the catalyst system of $SbCl_5$, $Me_3SiCl$ and $SnI_2$.

Now, we would like to demonstrate the scope of the above reaction and the stereoselective syntheses of (-)-cis-rose oxide (1) and (cis-6-methyltetrahydropyran-2-yl)acetic acid (2), the glandular secretion of the civet cat (***Viverra civetta***).[2]

First, we examined the reaction of various methyl substituted lactones in order to investigate the effect of substituent on the stereocontrol (Table 1).[3]

Tetrahydropyrans and oxepanes were prepared stereoselectively on the successive treatment of δ-valerolactones and ε-caprolactones with t-butyldimetylsiloxy-1-ethoxyethene and silyl nucleophiles, respectively, in the presence of a catalytic amount of $TrSbCl_6$ or a catalyst system of $SbCl_5$, $Me_3SiCl$ and $SnI_2$.

In the case of δ-lactones, silyl nucleophiles mainly attack the oxonium intermediate (6a-d), a major conformer initially formed from the lactone and t-butyldimethylsiloxy-1-ethoxyethene, from the α-side due to tortional strain (Fig. 1.). The stereoselectivity is especially high in the case of 3- and 5-methylvalerolactones (3d,f) (entries 5, 7, and 8), because silyl nucleophiles attack from the α-side of the initially formed oxonium intermediate (7b,d), a minor conformer, as well due to 1,3-diaxial interaction. On the other hand, in the case of 2- and 4-methylvalerolactones (3c,e) (entries 3, 4, and 6), the nucleophile attack takes place mainly from the α-side of the intermediate (6a,c), however, the decrease in the selectivity may be depend on the β-side attack of

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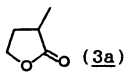
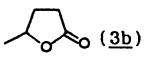
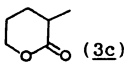
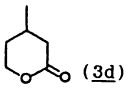
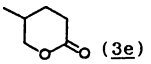
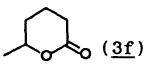
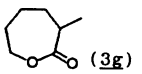
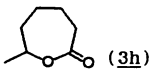
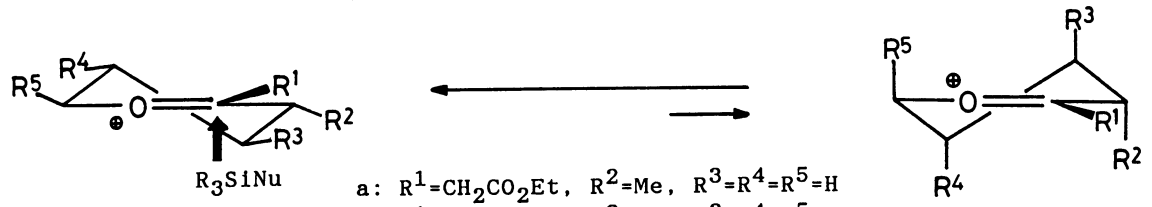
Scheme 1.

Table 1. Substituent Effect of Lactones

| Entry | 3 | $R_3SiNu$ | Yield / % (cis/trans)[a] Method A[b] | Method B[c] |
|---|---|---|---|---|
| 1 |  (3a) | $Et_3SiH$ | 71 (36:64) | 56 (31:69)[d] |
| 2 |  (3b) | $Et_3SiH$ | 59 (53:47) | 39 (48:52)[d] |
| 3 |  (3c) | $Et_3SiH$ | 84 (12:88) | 83 (10:90)[e] |
| 4 | 3c | $Me_3SiCH_2CH=CH_2$ | 40 (17:83)[f] | 45 (26:74)[d,g] |
| 5 |  (3d) | $Et_3SiH$ | 82 (>99:1) | 89 (>99:1)[e] |
| 6 |  (3e) | $Et_3SiH$ | 87 (7:93) | 82 (4:96)[e] |
| 7 |  (3f) | $Et_3SiH$ | 82 (>99:1) | 79 (>99:1)[e] |
| 8 | 3f | $Me_3SiCH_2CH=CH_2$ | 86 (>99:1) | 76 (>99:1)[d] |
| 9 |  (3g) | $Et_3SiH$ | 91 (>99:1) | 86 (>99:1)[d] |
| 10 |  (3h) | $Et_3SiH$ | 85 (>99:1) | 81 (>99:1)[d] |

a) The selectivity was determined by 400-MHz $^1H$ NMR. b) $TrSbCl_6$ (10 mol%) was used as a catalyst. c) $SbCl_5$ combined with $Me_3SiCl$ (10 mol%) and $SnI_2$ (10 mol%) was used as a catalyst. d) 10 mol% of $SbCl_5$ was used. e) 5 mol% of $SbCl_5$ was used. f) 2-Ethoxycarbonylmethyl-2-hydroxy-3-metyltetrahydropyran (5) was obtained in 32% yield as by-product. g) 5 was obtained in 35% yield as by-product.

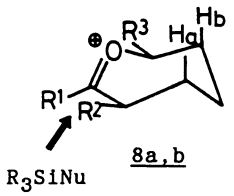
nucleophiles to the intermediate (7a,c). When 2-methylvalerolactone was employed, it was expected that cis isomer should be mainly obtained because conformer (7a) preferred to conformer (6a) due to allylic strain.[4] Surprisingly, however, the trans isomer was preferentially obtained probably due to a small allylic strain associated with conformer (6a).




a: $R^1$=$CH_2CO_2Et$, $R^2$=Me, $R^3$=$R^4$=$R^5$=H
b: $R^1$=$CH_2CO_2Et$, $R^3$=Me, $R^2$=$R^4$=$R^5$=H
c: $R^1$=$CH_2CO_2Et$, $R^4$=Me, $R^2$=$R^3$=$R^5$=H
d: $R^1$=$CH_2CO_2Et$, $R^5$=Me, $R^2$=$R^3$=$R^4$=H

Fig. 1.

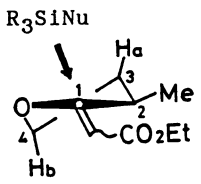
As for $\varepsilon$-lactones, it is supposed that the $\beta$-side of the oxonium intermediate (8a,b) is blocked by the axial hydrogens $H_a$ and $H_b$, located at the 4- and 6-position, respectively, like the endo side of norbonylene (Fig. 2.).[5] Actually, the silyl nucleophile attacks from the $\alpha$-side to give cis isomers from 2- and 6-methylcaprolactones (3g,h) (entries 9 and 10). We previously described that in the case of $\gamma$-butyrolactone, the elimination of t-butyldimethylsilanol from silylated cyclic hemiketal took place readily to give 2-ethoxycarbonylmethylidenetetrahydrofuran.[1] Accordingly, we suppose that the silyl nucleophile attacks the intermediate, $\alpha,\beta$-unsaturated esters (9 and 10) derived respectively from 2- and 4-methylbutyrolactones (3a,b) (Fig. 3.).[6] In the former case (entry 1), the trans isomer was obtained in preference to the cis isomer due to the 1,3-diaxial interaction because $H_b$ is closer to $C^1$ than $H_a$ in 9. In the latter case (entry 2), the nucleophile would attack from both sides because there is little difference in the distances $C^1$-$H_a$ and $C^1$-$H_b$ in 10.




8a,b

a: $R^1$=$CH_2CO_2Et$, $R^2$=Me, $R^3$=H
b: $R^1$=$CH_2CO_2Et$, $R^3$=Me, $R^2$=H

Fig. 2.

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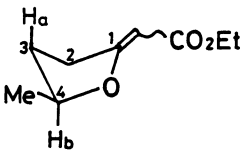


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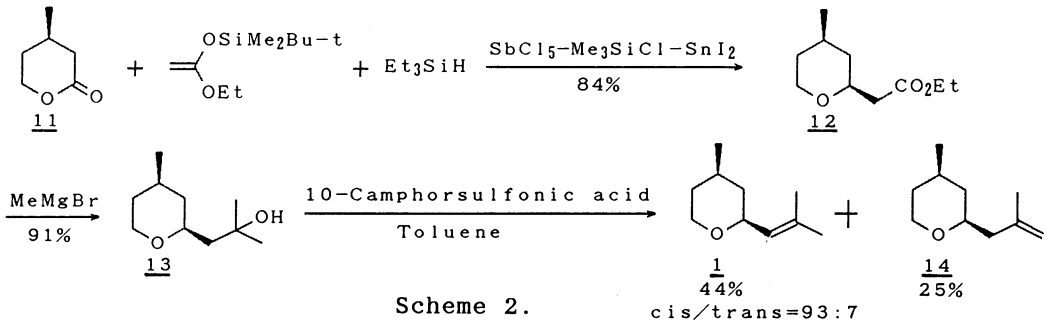
Fig. 3.

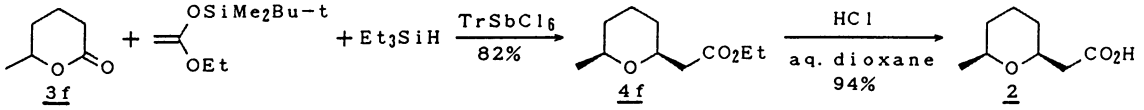
Next, (-)-cis-rose oxide (1) and (cis-6-methyltetrahydropyran-2-yl)acetic acid (2) were stereoselectively synthesized by utilizing the present reaction.

(R)-3-Methylvalerolactone (11), prepared according to the method of R. Rossi, A. Carpita and M. Chini,[7] reacted with t-butyldimethylsiloxy-1-ethoxyethene and triethylsilane in the presence of a catalyst system of $SbCl_5$, $Me_3SiCl$ and $SnI_2$ to afford (2S,4R)-2-ethoxycarbonylmethyl-4-methyltetrahydropyran (cis/trans=>99:1) (12) in 84% yield. The Grignard reaction of the ester (12) with methylmagnesium bromide afforded the tertiary alcohol (cis/trans=>99:1) (13) in 91% yield, which in turn underwent acid-catalyzed dehydration (dl-10-camphorsulfonic acid / toluene, reflux) to afford (-)-cis-rose oxide (cis/trans=93:7) (1), $[a]_D^{20}$-68.3° (c 3.0, $CHCl_3$) (lit.[8] $[a]_D$-58.1°), in 44% yield, along with (2S,4R)-4-methyl-2-(2-methyl-2-propenyl)-tetrahydropyran (cis/trans=>99:1) (14), $[a]_D^{20}$-7.9° (c 3.0, $CHCl_3$), in 25% yield (Scheme 2.).




Scheme 2.

(cis-2-Ethoxycarbonylmethyl-6-methyltetrahydropyran (4f) was prepared in 82% yield by the reaction of 5-methylvalerolactone (3f) with t-butyldimethylsiloxy-1-ethoxyethene and triethylsilane in the presence of a catalytic amount of $TrSbCl_6$. The tetrahydropyran (4f) was hydrolyzed under acidic condition to give (cis-6-methyltetrahydropyran-2-yl)acetic acid (2),[9] mp 51-53 °C (lit.[2] 52-53 °C), in 94% yield (Scheme 3.).




Scheme 3.

References

1) T. Mukaiyama, K. Homma, and H. Takenoshita, Chem. Lett., 1988, 1725.

2) B. Maurer, A. Grieder, and W. Thommen, Helv. Chim. Acta, 62, 44 (1979).

3) Except for 4g, the stereochemistry was determined by the NOE analysis (400-MHz NMR spectrum) and/or by the spin-spin coupling constants for the ring protons. The stereochemistry of 4g was determined by X-ray analysis for α-naphthyl urethane of cis-2-(2-hydroxyethyl)-3-methyloxepane, derived from 4g via reduction with lithium aluminum hydride.

4) This stereoselectivity is opposite to that of the reduction of 2-hydroxy-3-methyl-2-phenyltetrahydropyran with $Et_3SiH$ in the presence of trifluoroacetic acid; G. A. Kraus, M. T. Molina, and J. A. Walling, J. Org. Chem., 52, 1273 (1987).

5) We assume that the most stable conformation of oxonium intermediate (8a,b) resembles that of cycloheptene. Molecular mechanics calculations for cycloheptene indicate the following steric energy order:

6) We assume that the most stable conformations of 9 and 10 resemble those of methyl substituted 2-methylidenetetrahydrofurans indicated by molecular mechanics calculations.

7) R. Rossi, A. Carpita, and M. Chini, Tetrahedron, 41, 627 (1985).

8) T. Ogawa, N. Takasaka, and M. Matsui, Carbohydrate Research, 60, C4 (1978).

9) No stereoisomer was detected by either $^1H$ or $^{13}C$ NMR.

( Received March 9, 1989 )