CHEMISTRY LETTERS, pp. 1621-1624, 1981.

HIGHLY STEREOSELECTIVE CONSTRUCTION OF CHIRAL QUATERNARY CARBON: ASYMMETRIC SYNTHESIS OF β,β-DISUBSTITUTED γ-BUTYROLACTONES

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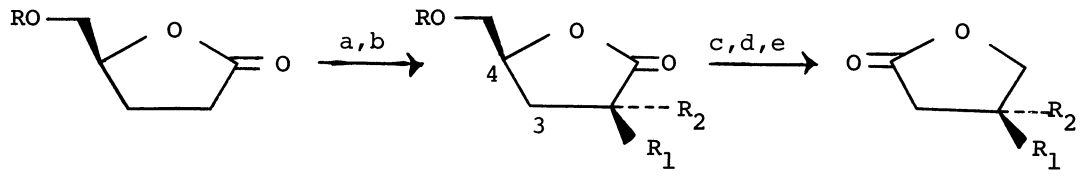
Asymmetric synthesis of β,β-disubstituted γ-butyrolactones was carried out in highly stereoselective and predictable way, by means of sequential dialkylation of (S)-γ-trityloxymethyl-γ-butyrolactone followed by lactone carbonyl transposition. Application to the synthesis of spirocyclic compound was also described.

In these ten years great progresses have been reported in the field of asymmetric synthesis.[2] There are, however, only a few reliable methods for the construction of chiral quaternary carbon centers fully substituted with alkyl groups.[3] As part of our research program directed toward the asymmetric total synthesis of natural products based on the novel application of easily available (S)-γ-hydroxymethyl-γ-butyrolactone (1) as a chiral synthon, we have reported the efficient asymmetric synthesis of α,β-disubstituted γ-butyrolactones.[4,5,6] Evaluating the increasing usefulness of γ-butyrolactone systems as synthetic intermediates,[7] we have now extended our studies to the development of the general and efficient asymmetric synthesis of β,β-disubstituted γ-butyrolactones by means of stereoselective sequential dialkylation of (S)-γ-trityloxymethyl-γ-butyrolactone (2) with two different electrophiles followed by the lactone carbonyl transposition procedure wherein the original chiral center was removed.[4,8] Particularly significant feature of this approach is that both enantiomers with predictable absolute configuration can be produced simply by inverting the introduction order of electrophiles.

Critical stage of the present synthesis is the sequential dialkylation of 2 with two different electrophiles leading to quaternary carbon compounds 3. Results are extremely promising as summarized in Table I. Typical procedure is as follows (Run 5). The lactone enolate, prepared from 2 (8.1 mmole) with LDA (1.2 eq) and HMPA (1.2 eq) in THF (20 ml) at -78° under argon, was treated with ethyl iodide (1.1 eq) for 4h. After addition of LDA (1.2 eq) and HMPA (1.2 eq) to the above mixture (-78°, 0.5h), methyl iodide (1.4 eq) was added. The whole was stirred at -78° for 5h. Usual work-up followed by the treatment of crude product (3) in acidic methanol for 10h gave the detritylated alcohol, which was purified without fractionation by silica gel column chromatography (ether) to furnish cis-4 ($R_1=CH_2CH_3$, $R_2=CH_3$, 65%)[9] with the diastereomeric purity of over 99%.

Stereochemical course of the introduction of alkyl groups was found to be

Table 1. Synthesis of 4 and 5



1 R=H
2 R=CPh3

3 R=CPh3
4 R=H

5

a) LDA-HMPA, R_1X/THF, -78°, then LDA-HMPA, R_2X, -78°: R_1X and R_2X=CH_3I, CH_3CH_2I, $CH_3(CH_2)_2I$, CH_2=$CHCH_2Br$, $PhCH_2Br$. b) c.HCl-MeOH, rt. c) $LiAlH_4$/THF, rt. d) $NaIO_4/H_2O$-AcOEt, rt. e) Jones oxidation, rt.

			4			5	
Run	R_1	R_2	Yield(%)[a]	cis/trans[b]	$[\alpha]_D^{22}(CHCl_3)$	Yield(%)[c]	$[\alpha]_D^{24}(CHCl_3)$
1	CH_3	CH_3CH_2	59	1/>99	+20.8	53	-15.8[e]
2	CH_3	$CH_3(CH_2)_2$	49	3/>97	+22.6	44	-11.2
3	CH_3	CH_2=$CHCH_2$	53	2/>98	+12.2	43	-3.2
4	CH_3	$PhCH_2$	47	2/>98	-19.4	64	-8.51
5	CH_3CH_2	CH_3	65	>99/1	+64.8	47	+16.1[e]
6	$CH_3(CH_2)_2$	CH_3	59[d]	>97/3	+23.7		
7	CH_2=$CHCH_2$	CH_3	47	>98/2	+88.7		
8	$PhCH_2$	CH_3	56	>96/4	+75.5	66	+8.57

a) Overall yield from 2. b) Diastereomeric ratio(cis/trans) was determined by HPLC, ^1H and ^{13}C NMR analysis. c) Overall yield from 4. d) Obtained by catalytic hydrogenation of the corresponding allyl derivative. e) Reported value for (S)-5 was $[\alpha]_D^{24}$+15.7°($CHCl_3$). See reference 10.

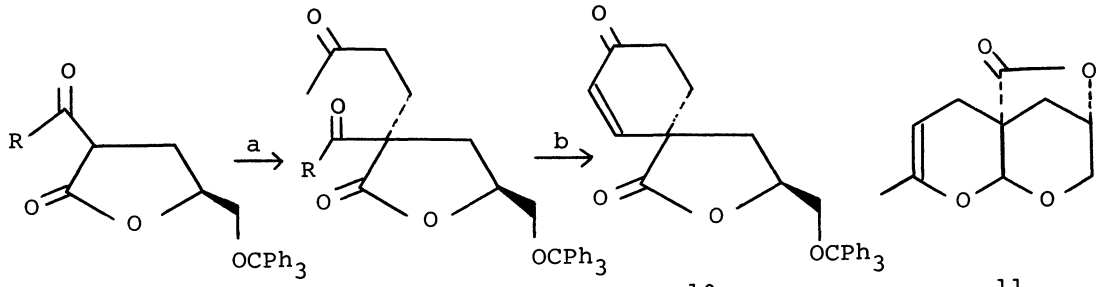
Table II. ^1H and ^{13}C NMR of 4

	R_2	CH_3CH_2		$CH_3(CH_2)_2$		CH_2=$CHCH_2$		$PhCH_2$	
Trans-4, R_1=CH_3	H-3(δ)	1.90	2.17	1.90	2.18	1.90	2.24	1.85	2.23
	$J_{3,4}$(Hz)	9	7	9	7	9	7	10	7
	H-4(δ)	4.50		4.48		4.50		3.5	
	2-CH_3(δ)	22.9		23.5		23.4		25.0	
	R_1	CH_3CH_2		$CH_3(CH_2)_2$		CH_2=$CHCH_2$		$PhCH_2$	
Cis-4, R_2=CH_3	H-3(δ)	1.88	2.07	1.88	2.12	1.83	2.12	1.76	2.11
	$J_{3,4}$(Hz)	7	9	7	10	7	11	6	10
	H-4(δ)	4.55		4.55		4.52		4.48	
	2-CH_3(δ)	22.6		23.1		23.1		23.3	

highly controlled under the influence of the trityloxymethyl group. Introduction of ethyl and then methyl group produced, after lactone carbonyl transposition procedure ($LiAlH_4$, $NaIO_4$, then Jones oxidation)[4], optically pure (+)-5 (R_1=CH_3CH_2 R_2=CH_3)($[\alpha]_D^{24}$+16.1°($CHCl_3$), reported[10] $[\alpha]_D^{24}$+15.7°($CHCl_3$)) having S-configuration (Run 5). On the other hand, inversion of the introduction order gave (-)-5 (R_1=CH_3, R_2=CH_3CH_2)($[\alpha]_D^{24}$-15.8°($CHCl_3$)) having R-configuration (Run 1). As the absolute configuration of optically active 5 is well established, these facts are clearly consistent with the expectation that alkylation would preferentially occur from the face of lactone enolate opposite to trityloxymethyl group.

The stereochemical course of the introduction was also supported by NMR (^1H, ^{13}C) analysis of 4 as shown in Table II. In the compounds synthesized by the introduction of methyl group at first, vicinal coupling constants ($J_{3,4}$) between H-4 and H-3 appearing at the higher field are larger than those between H-4 and H-3 appearing at the lower field. In the case of 4 (R_1=CH_3, R_2=CH_2Ph) large anisotropic effect on H-4 (δ3.5 ppm) was observed. These data clearly indicate that these compounds have the same relative configuration, that is, trans-configuration. In the cis-4 (R_2=CH_3), $J_{3,4}$ are also characteristic, showing the opposite trend to that of trans-4.[11] ^{13}C-NMR spectra were also characteristic, in which 2-CH_3 signals of cis-4 appeared at the slightly upfield than those of trans-4, probably due to the existence of weak γ-type effect.[12]

Extention of the above selective alkylation to Michael reaction could open the efficient access to the spirocyclic compound. Michael reaction of 6, prepared from 2 in the usual way, with methyl vinyl ketone in the presence of catalytic amount of base at room temperature gave 7 (mp 122-123°, $[\alpha]_D^{20}$+9.48°($CHCl_3$)) as the major product of the diastereomeric mixture (82:18) in 65% overall yield from 2. Similarly 8 was converted to 9 ($[\alpha]_D^{20}$+33.6°($CHCl_3$)) as the major product of the mixture (83:17) in 86% yield. The major stereochemical course of the Michael reaction was also shown to be the same as that of alkylation by converting 9 into 11 (p-TsOH /benzene) in 58% yield. Then 9 was treated with K_2CO_3 (5 eq) in the



6 R=OCH_2CH_3 7 R=OCH_2CH_3 10 11

8 R=H 9 R=H

a) For 6: $CH_3COCH=CH_2$, NEt_3/benzene, rt. For 8: $CH_3COCH=CH_2$, t-BuOK/t-BuOH-toluene, rt. b) K_2CO_3, n-Bu_4NBr/benzene, reflux.

presence of catalytic amount of n-Bu_4NBr in refluxing benzene for 4h to afford the optically pure spirocyclic lactone (10) ($[\alpha]_D^{20}$-11.1°($CHCl_3$)) in 65% yield.

The procedure described above give promise for construction of chiral quaternary carbon center having the appropriately functionalized alkyl substituents. Application to the asymmetric total synthesis of pharmacologically potent natural products is now in progress.

REFERENCES

1. Visiting professor from Seoul National University, Korea.
2. a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice Hall, New Jersey, 1971; b) A. I. Meyers, Acc. Chem. Res., 11, 375(1978); c) J. W. ApSimon and R. P. Seguin, Tetrahedron, 35, 2797(1979).
3. a) Review for the synthesis of quaternary carbon centers. S. F. Martin, Tetrahedron, 36, 419(1980); b) S. Hashimoto and K. Koga, Chem. Pharm. Bull.(Tokyo), 27, 2760(1979); c) H. Kogen, K. Tomioka, S. Hashimoto, and K. Koga, Tetrahedron Letters, 21, 4005(1980); d) G. Frater, ibid., 22, 425(1981).
4. a) K. Tomioka, H. Mizuguchi, and K. Koga, Tetrahedron Letters, 4687(1978); b) K. Tomioka and K. Koga, ibid., 3315(1979); c) K. Tomioka, T. Ishiguro, and K. Koga, J. Chem. Soc. Chem. Commun., 652(1979); d) idem, Tetrahedron Letters, 21, 2973(1980).
5. For the similar application of 2 to the synthesis of natural products by other research groups. a) J. P. Robin, O. Gringore, and E. Brown, Tetrahedron letters, 21, 2709(1980); b) S. Takano, M. Yonaga, K. Chiba, and K. Ogasawara, ibid., 21, 3697(1980).
6. For the other asymmetric synthesis of α-, or β-monosubstituted γ-lactones. a) reference 2b; b) K. Achiwa, Heterocycles, 12, 515(1979); c) T. Takeda and T. Mukaiyama, Chem. Lett., 163(1980).
7. a) B. M. Trost and T. P. Klun, J. Am. Chem. Soc., 101, 6756(1979); b) idem, J. Org. Chem., 45, 4256(1980); c) R. K. Boeckman, Jr., P. C. Naegely, and S. D. Arthur, ibid., 45,754(1980).
8. Quite recently similar attractive approach was reported by Prof. Takano and his coworkers. a) S. Takano, K. Chiba, M. Yonaga, and K. Ogasawara, J. Chem. Soc. Chem. Commun., 616(1980); b) S. Takano, C. Kasahara, and K. Ogasawara, ibid., 637(1981).
9. Satisfactory analytical data were obtained for all new compounds.
10. H. Ledo, G. Linstrumelle, and S. Julia, Tetrahedron Letters, 25(1975).
11. S. A. M. T. Hussain, W. D. Ollis, C. Smith, and J. F. Stoddart, J. Chem. Soc. Perkin 1, 1481(1975).
12. E. Wenkert, H. E. Gottlieb, O. R. Gottlieb, M. O. Das. Pereira, and M. D. Formiga, Phytochemistry, 15, 1547(1976).

(Received September 21, 1981)