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ASYMMETRIC CONJUGATE ADDITION REACTION BY THE USE OF (S)-γ-TRITYLOXYMETHYL-γ-BUTYROLACTAM AS A CHIRAL AUXILIARY

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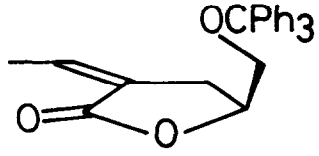
Summary: (S)-γ-Trityloxymethyl-γ-butyrolactam (**2**) serves as a chiral auxiliary in the conjugate addition reaction of the corresponding imide (**3**) of α,β-unsaturated carboxylic acids with Grignard reagents in the presence of $CuBr\text{-}SMe_2$ in THF to give, after hydrolysis, the β,β-disubstituted carboxylic acids (**5**) with predictable absolute configuration and high enantiomeric excess.

There has been a considerable challenge directed toward the asymmetric conjugate addition reaction of α,β-unsaturated carbonyl compounds.[1] Previously we have reported highly stereoselective conjugate addition reaction of lithiated dithioacetal with optically pure butenolide (**1**) in which trityloxymethyl group takes nearly axial conformation and one of the benzene rings covers the β-face of **1**, permitting the preferential nucleophile attack from the α-face.[2] The reason why the bulky trityloxymethyl group in **1** takes the axial conformation is not clear, however, it is highly probable that the HOMO-LUMO orbital interaction between the lone pair of ether oxygen and antibonding orbital of the O-C sigma bond of the butenolide ring would be anticipated in the stabilization of the conformation. The next stage of our investigations is to visualize that fixing conformation by orbital interaction provides a basic concept in the design of new chiral auxiliary. We report here that (S)-γ-trityloxymethyl-γ-butyrolactam (**2**)



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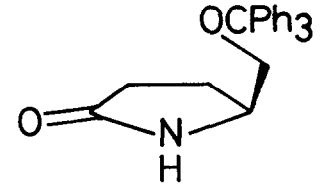

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serves as an efficient chiral auxiliary in the asymmetric conjugate addition reaction of the corresponding imides (**3**) of α,β-unsaturated carboxylic acids. The trityloxymethyl group in **3** takes the similar axial conformation as in the case of the butenolide (**1**), allowing the attack

of nucleophile from the α-face of **3** to give **4**. The adducts (**4**) are hydrolyzed to provide the corresponding β,β-disubstituted carboxylic acids (**5**) with predictable absolute configuration and high enantiomeric excess (ee).

The chiral auxiliary (**2**) (mp 165.5-166°C, $[\alpha]_D^{20}$ +13.7°($CHCl_3$)) was prepared in 89% yield by tritylation (Ph_3CCl, NEt_3, DMAP in CH_2Cl_2) of the corresponding lactam alcohol,[3] prepared in two steps from L-glutamic acid, one of the most inexpensive commercially available optically active compounds.[4] The lactam ether (**2**) was then acylated to the imide (**3**: R^1=Me, 86%, mp 116.5-117°C, $[\alpha]_D^{20}$ -86.2°($CHCl_3$); R^1=Bu, 96%, oil, $[\alpha]_D^{25}$ -64.5°($CHCl_3$)) according to the Evans procedure (i. BuLi in THF; ii. acid chloride).[5]

The conformation of **2** and **3** in $CDCl_3$ were analyzed by 400 MHz ^{1}H NMR.[6] Coupling constants between the methylene protons of the trityloxymethyl group and the methine proton of the lactam ring are 4.5 and 7.5 Hz, respectively, indicating that the trityloxymethyl group does not take the expected conformation in the γ-lactam (**2**). Fortunately, acylation of the lactam NH changes the situation, and in the imide (**3**: R^1=Me) coupling constants between the methylene protons and methine proton are 2.8 and 3.9 Hz, respectively, indicating that C-O and C-H bonds take the desired anti-relationships as shown in **6**. Furthermore, the coupling constants between the methine proton and ring methylene protons are 8.8 and 1.4 Hz, supporting that the trityloxymethyl group takes the required axial conformation. It is interesting to consider the reason why the trityloxymethyl group takes the axial conformation in the imide (**3**) and does not take in the lactam (**2**). The lowering the energy level of antibonding orbital of C-N sigma bond, so called LUMO, by acylation of the lactam NH should make the effective interaction possible to occur with the lone pair orbital of the oxygen of trityl ether as shown in **7**.

Conjugate additions to **3** were studied using Grignard reagent in the presence of CuBr-SMe_2 and diorganocopperlithium. The imide **3** (R^1=Me) was treated with phenylmagnesium chloride in the presence of CuBr-SMe_2 in THF at -23°C to give the adduct **4** (R^1=Me, R^2=Ph) in 95% diastereomeric excess (de).[7] Hydrolysis of the adduct (**4**) afforded (S)-3-phenylbutyric acid (**5**) in 94% ee.[8] Use of diphenylcopperlithium in ether decreased the diastereoselectivity to give **4** in 67% de and the corresponding acid of 70% ee was obtained. The high diastereoselectivity observed by the use of organomagnesium species of more coordinating ability than organolithium[9] is attributable to the fixing both carbonyls to form the syn-s-cis form of the imide (**3**) which will be equilibrated with anti-s-cis form (**8**),[10,11] and preferential attacking of nucleophile from the α-face of **3**. Some of the results are summarized in the Table I.

Typical procedure is as follows (for (S)-3-phenylbutyric acid (**5**: R^1=Me, R^2=Ph)). A THF solution of PhMgCl (1.2M, 3.75 ml, 4.5 mmol) was added to a solution of Me_2S-CuBr (462 mg, 2.25 mmol) in a mixture of THF (15 ml) and Me_2S (6 ml) at -48°C. After 10 min stirring at -23°C a solution of **3** (R^1=Me, 636 mg, 1.5 mmol) in THF (3 ml) was added and the whole was stirred for 1.5 h at -23°C. Standard work-up and silica gel chromatography (hexane-AcOEt/7:1) afforded **4** (R^1=Me, R^2=Ph; 737 mg, 98%) as a colorless viscous oil. Diastereomeric excess of 95% was determined by HPLC analysis (silica gel, Waters Associates, Inc., RADIAL-PAK B, 254 nm, hexane-AcOEt/14:1, 2 ml/min).

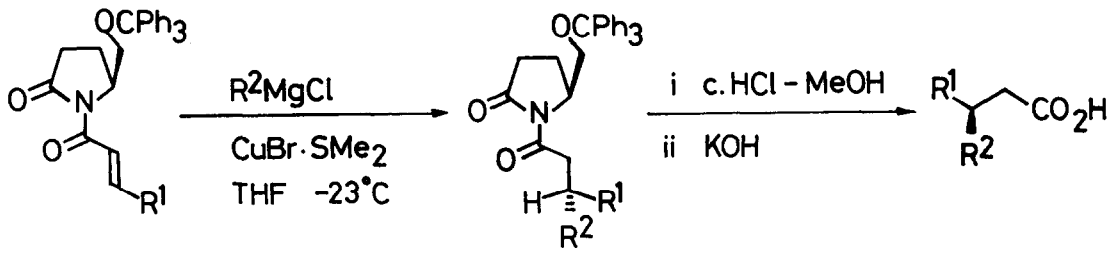
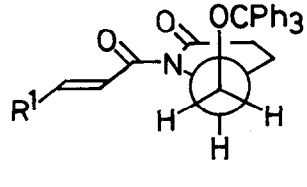


Table I. Asymmetric Conjugate Addition Reactions of The Chiral Imides (3)

3		4		5			
R^1	R^2MgCl	Yield (%)	de (%)	Yield (%)	ee (%)	$[\alpha]_D$ (°)	$[\alpha]_D$ (°)[lit]
Me	p-Tol	98	91	85	89 (S)	+57.9(PhH)	+65[a]
Me	Ph	98	95	89	94 (S)	+53.5(PhH)	+57.23[b]
Me	c-Hex	97	87	88	77 (S)[c]	-2.01(neat)	
Me	Bu	97	91	91	92 (R)	+3.87(neat)	-4.21[d]
Me	Et	90		75	80 (R)	-6.53(neat)	-8.15[e]
Me	Vinyl	62	88	82	88 (S)	+15.3($CHCl_3$)	+17.3[f]
Bu	Ph	80		77	96 (S)	+35.6(PhH)[h]	+37.05[g,h]
Bu	c-Hex	90		76	97 (S)	+5.76(neat)	-5.96[b]
Bu	Et	77	81	88	81 (S)	-2.37(neat)	+2.94[b]
Bu	Vinyl	60	84[i]	90	85 (S)[j]	-3.93($CHCl_3$)	

a) V. K. Honwad and A. S. Rao, Tetrahedron, **20**, 2921 (1964). b) A. I. Meyers, R. K. Smith, and C. E. Whitten, J. Org. Chem., **44**, 2250 (1979). c) Determined by reduction of the acid to the corresponding alcohol. S. Hashimoto, S. Yamada, and K. Koga, Chem. Pharm. Bull., **27**, 771 (1979). d) P. A. Levene and R. E. Marker, J. Biol. Chem., **95**, 1 (1932). e) C. G. Overberger and I. Cho, J. Org. Chem., **33**, 3321 (1968). f) T. Uematsu, T. Umemura, and K. Mori, Agric. Biol. Chem., **47**, 597 (1983). g) T. Mukaiyama and N. Iwasawa, Chemistry Lett., **1981**, 913. h) Measured at 577 nm instead of D line. i) Determined by reduction to the corresponding imide (**4**: R_1=Bu, R_2=Et). j) Determined by reduction to the corresponding carboxylic acid (**5**: R_1=Bu, R_2=Et).



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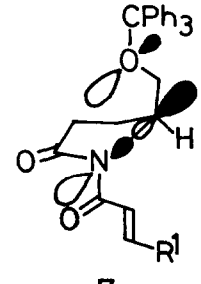

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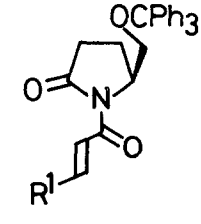

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A solution of **4** (737 mg) obtained above in MeOH (10 ml) and c. HCl (0.4 ml) was refluxed for 12 h and then a solution of KOH (0.5 g) in water (2 ml) was added. The whole was refluxed for 5 h. Usual work-up and silica gel chromatography (or bulb-to-bulb distillation) afforded (S)-3-phenylbutyric acid (214 mg, 89%) in 94% ee. If necessary, the γ-lactam alcohol is recoverable for reuse without any loss of optical purity at the step of acid hydrolysis.

It is important to note that β,β-disubstituted carboxylic acids (**5**) are produced in a good to excellent ee and the absolute configuration of **5** is reasonably predictable.

Application of the chiral auxiliary **2** to the other type of asymmetric reactions is the subject of the current studies.

References and Notes

1. Reviews: K. Tomioka and K. Koga, "Asymmetric Synthesis," ed. by J. D. Morrison, Academic Press, New York, Vol. 2 (1983) p.201; G. H. Posner, ibid., Vol. 2 (1983) p.225; K. A. Lutomoski and A. I. Meyers, ibid., Vol. 3 (1984) p.213.
   Leading references: W. Oppolzer, P. Dudfield, T. Stevenson, and T. Godel, Helv. Chim. Acta, **68**, 212 (1985); K. Soai, H. Machida, and A. Ookawa, J. Chem. Soc., Chem. Commun., **1985**, 469; K. Tomioka, M. Sudani, Y. Shinmi, and K. Koga, Chemistry Lett., **1985**, 329; D. Enders and K. Papadopoulos, Tetrahedron Lett., **24**, 4967 (1983); F. Leyendecker and D. Laucher, ibid., **24**, 3517 (1983); D. J. Cram and G. D. Y. Sogah, J. Chem. Soc., Chem. Commun., **1981**, 625.
2. K. Tomioka, H. Kawasaki, Y. Iitaka, and K. Koga, Tetrahedron Lett., **26**, 903 (1985); K. Tomioka, H. Kawasaki, and K. Koga, ibid., **26**, 3027 (1985).
3. R. B. Silverman and M. A. Levy, J. Org. Chem., **45**, 815 (1980).
4. All new compounds described in this paper provided the satisfactory spectroscopic and analytical data.
5. D. A. Evans, J. Bartroli, and T. L. Shih, J. Am. Chem. Soc., **103**, 2127 (1981).
6. The authors are grateful to Professors Y. Murakami and Y. Yokoyama, Faculty of Pharmaceutical Sciences, Toho University, for taking 400 MHz NMR.
7. Diastereomeric excess was determined by HPLC analysis.
8. Enantiomeric excess was determined by the optical rotation. See the Table I.
9. W. C. Still and J. H. McDonald, III, Tetrahedron Lett., **21**, 1031 (1980).
10. The structure of the imides has been reported. E. A. Noe and M. Raban, J. Am. Chem. Soc., **97**, 5811 (1975); C. M. Lee and W. D. Kumler, ibid., **84**, 565 (1962).
11. α,β-Unsaturated tertiary amides have been reported to be predominantly in the s-cis form. G. Montaudo, V. Librando, S. Caccamese, and P. Maravigna, J. Am. Chem. Soc., **95**, 6365 (1973).

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