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ENANTIOSELECTIVE DEPROTONATION OF THE MONOACETALS OF BICYCLO[3.3.0]OCTAN-3,7-DIONE. AN APPROACH TO THE ASYMMETRIC SYNTHESIS OF CHIRAL SYNTHONS FOR CARBACYCLINS

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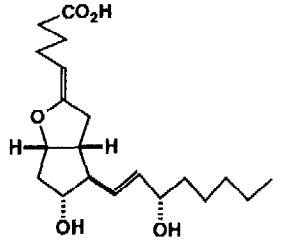
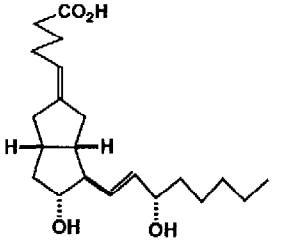
Summary: Kinetic deprotonation of the monoacetals (**4**) of bicyclo[3.3.0]octan-3,7-dione by chiral lithium amides (**5**) in the presence of excess trimethylsilyl chloride afforded the corresponding silyl enol ethers (**6**), useful synthons for the synthesis of optically active carbacyclins, in up to 94% ee.

Since the discovery of prostacyclin (**1**),[1] a potent inhibitor of platelet aggregation and a potent vasodilator, a great variety of structurally modified analogs have been synthesized to obtain chemically stable mimics having similar biological activities.[2] Carbacyclin (**2**), a carbocyclic analog of **1**, and its derivatives have attracted much attention in this respect, and have been targets of many synthetic efforts. For the synthesis of optically active **2**, several kinds of optically active starting materials, such as a resolved cyclobutanone derivative,[3a] Corey lactone and its derivative,[3b,c] and a resolved monoacetal (**3**) of bicyclo[3.3.0]octan-3,7-dione derivative,[3d] have been employed.



1



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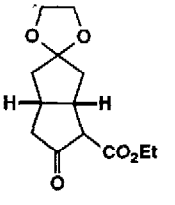
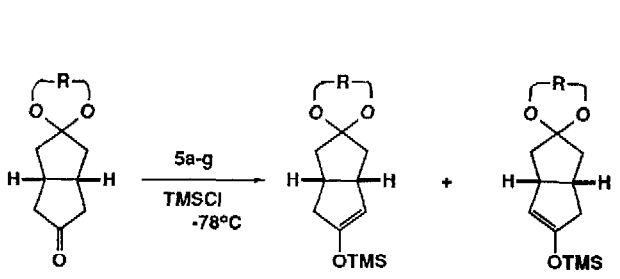


(1S,5R)-**3**

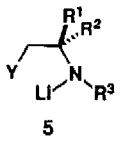
We have previously reported that kinetic deprotonation of prochiral 4-substituted cyclohexanones by chiral lithium amides occurs enantioselectively in the presence of excess trimethylsilyl chloride (TMSCl) to give the corresponding trimethylsilyl enol ethers in reasonably high ee.[4] Recognizing the presence of a plane of symmetry in monoacetals (**4**) of bicyclo[3.3.0]octan-3,7-dione as in 4-substituted cyclohexanones, it seems possible to deprotonate **4** enantioselectively by the same strategy using chiral lithium amides (**5**) to give the corresponding silyl enol ethers (**6**), which should be easily converted to optically active **3**.



4 (1S,5R)-6 (1R,5S)-6

a -R- = -CH_2CH_2-

b -R- = -$CH_2C(Me)_2CH_2$-

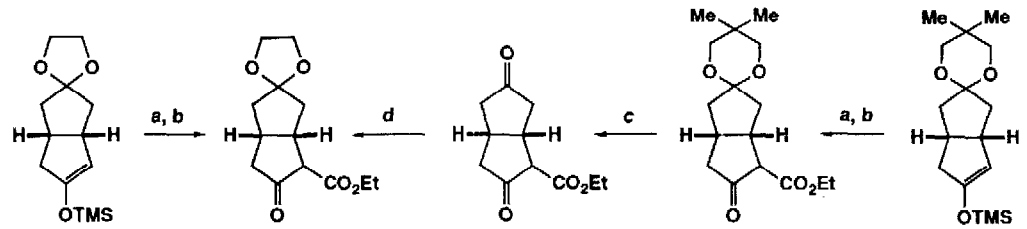


5

	R^1	R^2	R^3	Y
a	H	Ph	Pr^i	H
b	H	Ph	$CH(Et)_2$	H
c	H	Ph	CH_2Bu^t	H
d	H	Ph	Bu^t	H
e	Ph	H	Pr^i	N-Me
f	Ph	H	CH_2Ph	N-Me
g	Ph	H	CH_2Bu^t	N-Me

The results are summarized in Table 1. A typical experimental procedure (run 15) is as follows. A solution of chiral lithium amide (**5g**) was prepared under argon atmosphere by adding a solution of n-butyllithium (1.0 mmol) in hexane (1.58 M solution) to a solution of the corresponding amine (1.1 mmol) in THF (10 ml) under stirring at -78°C for 30 min. Hexamethylphosphoric triamide (HMPA) (1.1 mmol) was added,[4] and the resulting solution was warmed to room temperature for 5 min, and then re-cooled to -78°C. To this solution were added TMSCl (5 mmol) quickly, and then a solution of monoacetal (**4b**) (115 mg, 0.50 mmol) in THF (5 ml) dropwise during 8 min, and the whole was stirred at -78°C for 20 min. After addition of triethylamine (2 ml) and saturated aqueous sodium bicarbonate (4 ml), the reaction mixture was allowed to warm to room temperature. Usual work-up by using pentane as an extracting solvent gave a crude product, which was purified by column chromatography (silica gel, pentane-ether (20:1)) followed by bulb-to-bulb distillation (230°C/2 mmHg) to give **6b** (142 mg, 93%) as a colorless liquid (a colorless solid in a freezer) of $[\alpha]_{365}^{25}$+27.0°(2.10, benzene).

Absolute configurations and maximum rotations of **6a** and **6b** were determined by chemical correlation to **3**[3d] as shown below.[5]



(1S,5R)-6a (1S,5R)-3 8 7 (1S,5R)-6b

a) MeLi, b) NC-CO_2Et, c) AcOH in aqueous THF, d) p-TsOH in a mixture of  and 

Table 1. Enantioselective Deprotonation of **4**[a)]

Run	Monoacetal **4**	Base **5**	equiv.[b)]	Solvent	TMSCl equiv.[b)]	HMPA equiv.[c)]	Silyl enol ether[d)] **6**	Yield(%)	ee(%)	Confign.
1	**4a**	**5a**	1.2	toluene	5.0	0	**6a**	20	2	1S,5R
2	**4a**	**5a**	1.2	Et_2O	5.0	0	**6a**	17	21	1S,5R
3	**4a**	**5a**	1.2	DME	5.0	0	**6a**	75	59	1S,5R
4	**4a**	**5a**	1.2	THF	5.0	0	**6a**	68	70	1S,5R
5	**4a**	**5a**	2.0	THF	5.0	0	**6a**	87	71	1S,5R
6	**4a**	**5a**	1.2	THF	5.0	3.0	**6a**	54	40	1S,5R
7	**4a**	**5b**	2.0	THF	5.0	0	**6a**	95	83	1S,5R
8	**4a**	**5c**	2.0	THF	5.0	0	**6a**	90	4	1S,5R
9	**4a**	**5d**	2.0	THF	5.0	0	**6a**	84	30	1S,5R
10	**4a**	**5e**	1.2	THF	5.0	1.0	**6a**	66	11	1R,5S
11	**4a**	**5f**	2.0	THF	5.0	1.0	**6a**	21	51	1R,5S
12[e)]	**4a**	**5g**	1.9	THF	4.8	0	**6a**	91	71	1R,5S
13[e)]	**4a**	**5g**	2.0	THF	5.0	1.0	**6a**	91	87	1R,5S
14	**4b**	**5b**	2.0	THF	5.0	0	**6b**	93	84	1S,5R
15	**4b**	**5g**	2.0	THF	10.0	1.0	**6b**	93	94	1R,5S

a) All reactions were carried out by Corey's internal quench method.[6)] For procedure, see text. b) Relative to **4**. c) Relative to **5**. d) Maximum rotations were calculated to be $[\alpha]_{365}^{26}$ -36.9°(3.11, benzene) for (1S,5R)-**6a**, and $[\alpha]_{365}^{25}$ -28.7°(2.00, benzene) for (1S,5R)-**6b**.[5)] e) Reaction was carried out at -100°C.

It is shown that enantioselective deprotonation of prochiral **4** by **5** to give optically active **6** is realized. In all cases examined, the stereochemical course of this deprotonation reaction was found to be the same as that observed for the reaction using 4-substituted cyclohexanones as substrates.[4)] Thus, by using chiral bases (**5a-d**) having no internal ligation site for lithium, (1S,5R)-enantiomers of **6** were obtained in excess. The degree of asymmetric induction is highly dependent on the solvent used, presumably due to aggregation of these bases in solution, and is highest in THF in the absence of HMPA. By using chiral bases (**5e-g**) having N-methylpiperazino group, (1R,5S)-enantiomers of **6** were obtained in excess. These bases are expected to exist in chelated forms, and the degree of asymmetric induction in THF is highest in the presence of HMPA, which is assumed to work as an external ligand for lithium to destroy aggregation.[4,7)] Among chiral bases examined, **5g** was found to be the best, giving **6a** and **6b** in high ee. It is shown that the substituent on amide nitrogen in **5** exhibits strong influence on the degree of asymmetric induction. Mechanistic details are under investigation.

As both enantiomeric forms of **5** are available in optically pure states,[8] the method outlined above represents a new and efficient approach to enantioselective asymmetric synthesis of **6**, which are useful as synthons for the synthesis of optically active carbacyclins.

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5) a) Optically pure (1S,5R)-**3** is reported to show $[\alpha]_D^{22}$ +25.2°(1.67, $CHCl_3$).[3d] b) Treatment of (1S,5R)-**6a**($[\alpha]_{365}^{25}$ -25.3°(2.82, benzene)) with methyllithium in THF at 0°C, followed by quenching with TMSCl in the presence of diisopropylamine at -78°C gave (1S,5R)-**6a**($[\alpha]_{365}^{25}$ -25.4°(2.58, benzene)). c) (1S,5R)-**6a**($[\alpha]_{365}^{26}$ -26.2°(3.11, benzene)) was converted to (1S,5R)-**3**($[\alpha]_D^{25}$ +17.8°(1.90, $CHCl_3$)), corresponding to be 71% ee. c) (1S,5R)-**6b**($[\alpha]_{365}^{25}$ -19.3°(2.00, benzene)) was converted via **7** and **8** to (1S,5R)-**3**($[\alpha]_D^{22}$ +16.9°(1.67, $CHCl_3$)), corresponding to be 67% ee.
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8) Chiral bases (**5**) were prepared from optically pure phenethylamine or phenylglycine.

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