Asymmetric Induction in Stereoselective Carbocyclization of Cyclohexanone Enamines

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Received 28 September 1998

Abstract: A highly enantioselective synthesis of bicyclo[3.3.1]nonane diketones **3-5** was accomplished by (*S*)- and (*R*)-2-methoxymethylpyrrolidine induced asymmetric cyclization of cyclohexanone enamines **1**,**2** in reaction with propenoyl chloride. A possible enantiodifferentiation reaction mechanism was suggested.

Key words: enamine cyclization, SMMP/RMMP asymmetric induction, bicyclo[3.3.1]nonanediones

Asymmetric induction has gained a very broad range of applications both in development of principles of asymmetric synthesis and practical applications.[1] (*S*)-2-Methoxymethylpyrrolidine ((*S*)-MMP) is a pioneer chiral auxiliary in chiral syntheses due to the fact that this reagent is relatively cheap and good asymmetric inductions are reached.[2] Synthesis using (*S*)-MMP enamines is one of the most powerful methods of asymmetric reactions though only a few cyclizations have been reported by Seebach and co-workers.[3] We wish to report here higly enantioselective carbocyclization reactions of (*S*)-and (*R*)-MMP cyclohexanone enamines with propenoyl chloride suggesting also a possible enantiodifferentiation mechanism. The reaction of cyclohexanone enamines with α,β-unsaturated acid chlorides has been shown to give racemates of chiral bicyclo[3.3.1]nonane structure,[4a-c] which is a key skeleton in hispidospermidin, huperzine A, sesquiterpenes trifarienols A and B, and some other natural and biologically valuable products.[5] Therefore the enantioselective carbocycle construction is important for the production of a variety of structural analogues of this framework.

The chiral enamines **1** and **2** were prepared from cyclohexanone and 4-methylcyclohexanone and (*S*)- or (*R*)-2-MMP under standard conditions[6] (TsOH, benzene, Dean-Stark trap) in an atmosphere of nitrogen to avoid addition of oxygen to the pyrrolidine enamines. Carbocyclization of the enamines was effected by a slow addition of a propenoyl (acryloyl) chloride solution in benzene to a boiling solution of enamine in benzene.[7] The conditions were similar to the reaction of morpholine enamines with α,β-unsaturated acid chlorides which has led to the carbocyclization.[4] However, since the MMP enamines were less reactive the optimum reaction conditions had to be established. It was found that the yield of the cyclization product increased at prolonged reaction time and lower concentration of enamine in a reaction mixture (Table 1).

Table 1. Cyclization conditions for enamines of (*S*/*R*)-2-methoxymethylpyrrolidine

Enamine	Enamine concn. [mmol/ml]	Addition of acid chloride rate [mmol/h]	Reaction temperature [°C]	Yield of purified product [%]
(*S*)-**1**	0.5	20	130-140	19
(*R*)-**1**	0.22	1.3	100-120	39
(*S*)-**2**	0.55	1.8	90-110	39
(*R*)-**2**	0.22	1.3	100-110	47

The diastereomeric and enantiomeric purity of the reaction products were analysed by chiral GLC, NMR and measurement of specific rotation angle. GLC analysis using a stationary phase modified with β-cyclodextrin of a reaction product of enamine (*S*)-**1** showed that (-)-bicyclo[3.3.1]nonane-2,9-dione (70% *ee*) was the main product.[8] A comparison of the specific rotation angle with an authentic sample obtained earlier by a semipreparative HPLC separation of the corresponding racemic mixture[9] and spectra proved that the product was the (1*R*,5*S*)-enantiomer **3a**. Using (*R*)-enamine the (1*S*,5*R*)-enantiomer **3b** was obtained with a higher enantiomeric excess (Table 2).

Enantiomeric 7-methyl-bicyclo[3.3.1]nonane-2,9-diones **4,5** were formed in the reaction of methylcyclohexanone enamines **2**. The main product was *exo*-methyl bicyclic diketone **4a** (diastereomeric excess 98% after purification).

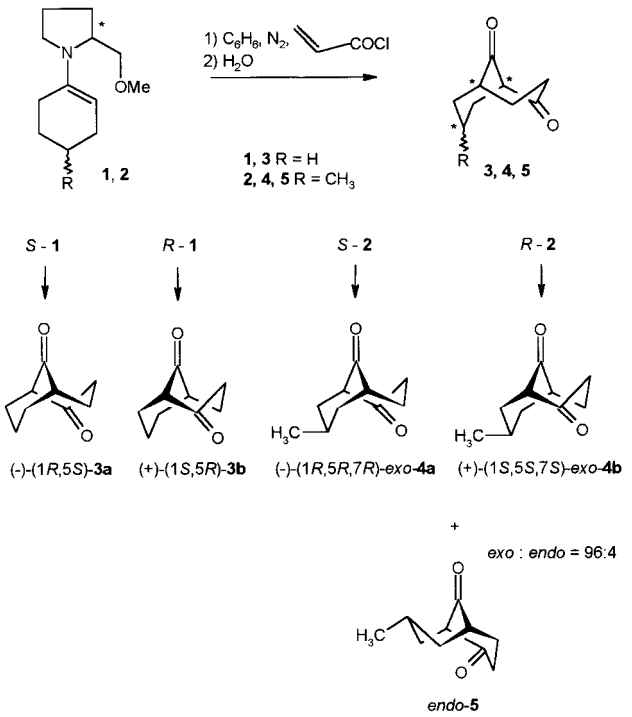
The *exo*-configuration of the methyl group was proved by a GLC and NMR comparison with the racemic sample obtained by a cyclization of the morpholine enamine with propenoyl chloride.[10] The minor diastereomer was not isolated from the reaction mixture. It is interesting to note that, again, the cyclization reaction of (*R*)-**2** enamine gave almost exclusively (+)-*exo*-diketone **4b** and also with higher *ee* compared to (*S*)-enamine. The asymmetric cyclization reaction results are presented in Scheme 1 and summarized in Table 2.

Three possible mechanisms of cyclization between enamines and α,β-unsaturated acid chlorides should be considered according to the literature data [4c,11]: 1. N-acylation of enamine and following [3,3] sigmatropic rearrangement leading to a highly reactive ketene participating in further cyclization, 2. Michael addition with subsequent cyclization - C-acylation and 3. a direct C-acylation following Michael addition. No obvious conclusion could be made from the previous investigations as to which one of the three mechanisms is occurring. It is also known that

Table 2. Asymmetric cyclization reaction of (*S*/*R*)-2-methoxymethylpyrrolidine enamines

Entry	Enamine	Product	Configuration	$[\alpha]^{D}_{20}$ (c,$CHCl_3$)	*ee* and *de* [%]
1	(*S*)-**1**	**3a**	1*R*,5*S*	-67.8° (0.005)	*ee* 70[a]
2	(*R*)-**1**	**3b**	1*S*,5*R*	+78.5° (0.005)	*ee* 81
3	(*S*)-**2**	**4a**	1*R*,5*R*,7*R*	-19.1°[b] (0.0048)	*de* 92, *ee* 83
4	(*R*)-**2**	**4b**	1*S*,5*S*,7*S*	+20.0° (0.0055)	*de* 99, *ee* 87

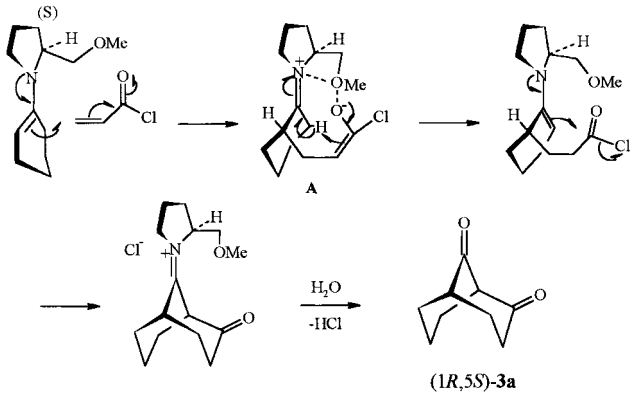
[a]GLC data; [b]>98% diastereomeric purity



Scheme 1

Michael addition of activated olefins to chiral 2-(methoxymethyl)pyrrolydine enamines is highly stereoselective.[12]

The stereochemical course of this reaction is controlled by the stereoelectronic effects, and the orientation of the methoxymethyl group is of significant importance to stereodifferentiation. Michael addition of propenoyl chloride to (*S*)-2-(methoxymethyl)pyrrolydine enamines occurs strictly from the heterotopic *Re*-face. Thus, the chiral center formed in a reaction of SMMP enamine has the (*S*)-configuration. On the contrary, addition to (*R*)-2-MMP enamines occurs from the *Si*-face and leads to the (*R*)-configuration of the chiral center. The reaction course in the case of cyclohexanone and (*S*)-2-(methoxymethyl)pyrrolydine enamine cyclization reaction with propenoyl chloride is shown in Scheme 2. The dipolar intermediate **A** involved in enamine Michael addition is stabilized by intramolecular solvation of the suitably oriented methoxymethyl group (cf. [13]). This stabilization is indicated by the dashed lines between a cationic nitrogen, a methoxy group oxygen, and a negatively charged oxygen in (*S*)-**A** intermediate (Scheme 2).



Scheme 2

In the case where the reaction follows any other of the mentioned pathways the methoxymethyl group could cause only some steric restrictions for reagent approach to the double bond of the enamine. Consequently, the chiral center formed during the first addition would have the opposite configuration and the enantiomeric purity of the obtained product would be low. The enantiomeric purity of bicyclo[3.3.1]nonane-2,9-diones **3a,b** synthesized in this work was ≥80%. The configuration of the first formed chiral center is in agreement with the stereochemical course of the Michael addition. The asymmetric cyclization reactions of chiral MMP and 4-methylcyclohexanone enamines were also highly diastereoselective. The *exo*-7-methylbicyclo[3.3.1]nonane-2,9-dione **4a** is the main diastereomer formed in both asymmetric and ordinary syntheses. This indicates that both reactions proceeded according to the same mechanism.

The above suggests that the Michael addition in the first step is dominating in cyclizations of MMP enamines with propenoyl chloride.

In summary, a highly enantioselective and diastereoselective synthesis of bicyclononane ketones via enamine cyclization reaction has been developed. The compounds have potential in the assembly of natural product skeletons.

Acknowledgement

We thank the Lithuanian Science and Studies Foundation for the financial support. We are grateful to Dr. U. Berg and Prof. T. Frejd for providing chiral GC facilities at Lund University.

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(6) **Synthesis of enamines, typical experimental procedure**: 0.026 mol of (S)-(+)-2-(methoxymethyl)pyrrolidine, 0.053 mol of cyclohexanone or 4-methyl cyclohexanone and a catalytic amount of p-toluenesulfonic acid in 35 ml of anhydrous benzene was refluxed under nitrogen using a Dean-Stark trap for 4-6 h. Benzene was evaporated and the residue distilled *in vacuo* under nitrogen. (2*S*)-1-(4-methylcyclohexen-1-yl)-2-(methoxymethyl)pyrrrolidine (*S*)-**1** b.p. 139-141°C/13mm Hg; (*R*)-**1**, b.p. 99-101°C/0.5 mm Hg. ^{1}H NMR (C_6D_6) δ 0.87-2.45 (m, 12H, H_2C), 2.6-3.8 (m, 5H, H_2C-O, H_2C-N, HC-N), 3.5 (s, 3H, H_3C-O), 4.5 (s, 1H, HC=). (*S*)-**2**, b.p. 116-117°C/4 mm Hg; (*R*)-**2**, b.p. 111-113°C/1 mm Hg. ^{1}H NMR ($CDCl_3$) δ 0.8-2.5 (m, 11H), 1.1 (d, 3H, H_3C-C, J 6.4Hz), 2.8-3.85 (m, 5H, H_2C-N, H_2C-O, HC-N), 3.4 (s, 3H, H_3C-O), 4.3 (s, 1H, HC=C).

(7) **Enamine cyclization, typical experimental procedure:** To a boiling solution of 0.01 mol enamine (*S*)-**1** in 20 ml of anhydrous benzene under nitrogen a solution of 0.01 mol propenoyl chloride in 10 ml anhydrous benzene was added over 2.5 h. Reaction mixture was heated at 130-140°C for 5 h. The mixture was cooled and the yellow precipitate was filtered off, washed with hexane, and hydrolysed with ice-cooled water overnight. Extractive workup with dichloromethane and distillation of the solvent gave a solid residue which was purified by sublimation at 90°C/2mm Hg. (1*R*,5*S*)-(-)-**3a**: $[\alpha]_D$ -67.8° (c 0.005 $CHCl_3$). GLC: t_R 9.93 min 150°C/4°C·min^{-1}/ 230°C. (1*S*,5*R*)-(+)-**3b**, $[\alpha]_D$ +78.5° (c 0.005 $CHCl_3$). GLC: t_R 9.92 min., 150°C/4°C·min^{-1} /230°C. ^{1}H NMR (D_2O) δ 1.25-2.57 (m, 8H, 4 H_2C), 2.62-2.78 (m, 3H, HC, H_2C-C=O), 3.06-3.13 (m, 1H, HC(-C=O)$_2$). (1*R*,5*R*,7*R*)-(-)-**4a** m.p. 47-48°C (from pentane-hexane); $[\alpha]_D$ -19.1° (c 0.0048 $CHCl_3$); GLC: t_R 12.34 min. 150°C/2°C·min^{-1}/190°C; (1*S*,5*S*,7*S*)-(+)-**4b** m.p. 50-51ºC (from pentane-hexane); $[\alpha]_D$+20.0° (c 0.0055 $CHCl_3$). ^{1}H NMR δ 0.92 (d, 3H, H_3C, J 6Hz) 1.5-2.9 (m, 10H), 3.06 (m, H1, HC(-C=O)$_2$); MS m/z (rel. intensity) 166 (89%, $M^{+\cdot}$), 151 (11%), 138 (9%), 124 (60%), 110 (43%), 95 (64%), 82 (29%), 77 (8%), 67 (33%), 55 (100%), 41 (18%); *endo*-**5**, t_R 14,63 min.; MS m/z 166 (88%, $M^{+\cdot}$), 151 (17%), 137 (4%), 124 (67%), 110 (41%), 96 (58%), 82 (26%), 77 (9%), 67 (30%), 55 (100%), 41 (20%).

(8) The *ee* was determined on a Perkin Elmer Autosystem gas chromatograph using 30m×25mm Alpha-Dex 120 or Beta-Dex 120 capillary columns (Supelco), carrier gas He (6.0 bar), split injector (1:100), flame ionisation detection.

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