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Novel Asymmetric Dealkoxycarbonylation of 3-Oxo-8-azabicyclo[3.2.1]-octane-2,4-dicarboxylates Using Porcine Liver Esterase: A New Route to (-)-Anhydroecgonine Methyl Ester

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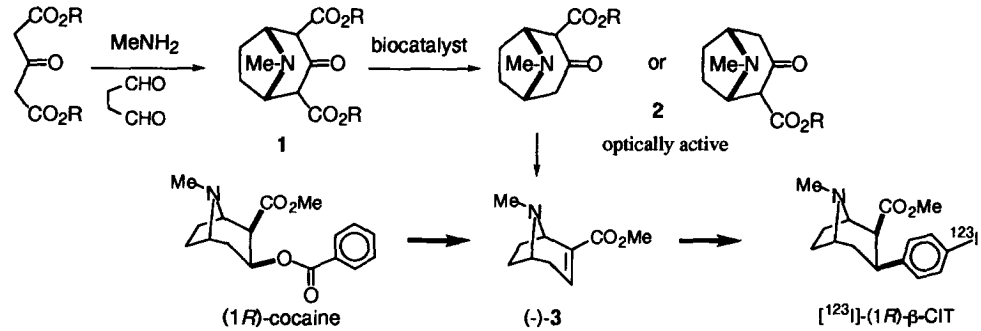
Abstract: The porcine liver esterase-catalyzed dealkoxycarbonylation of 8-benzyl-3-oxo-8-azabicyclo[3.2.1]octane-2,4-dicarboxylates (**4**) was found to give high enantiomeric excess of the desymmetrized keto ester (**5**). This novel dealkoxylcarbonylation opened a new route to the asymmetric synthesis of (1*R*)-cocaine related radiopharmaceuticals such as (1*R*)-β-CIT, for diagnosis of Parkinson's disease.

Keywords: Enzymic reaction, Decarboxylation, Hydrolysis, Alkaloids

We have recently described efforts for the exploitation of a novel lipase-catalyzed asymmetric demethoxycarbonylation of tetramethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate and for its application to the syntheses of (+)-carbacyclin, (-)-ajmalicine, (-)-tetrahydroalstonine, Corey lactone, (-)-isoiridomyrmecin, and (+)-loganin aglucon.[1] We have now turned our interest in the substrate of this demethoxycarbonylation from the bicyclo[3.3.0]octane skeleton to nitrogen-containing compounds, *i.e.*, 8-methyl-3-oxo-8-azabicyclo[3.2.1]octane-2,4-dicarboxylates (**1**) which are readily prepared by Robinson's tropinone synthesis[2] from succindialdehyde and a primary amine, and 1,3-acetonedicarboxylate in one step (high yields), because this skeleton is closely related to the cocaine related alkaloids, including radiopharmaceuticals, for diagnosis of Parkinson's disease.[3] The optically active radiopharmaceuticals related to cocaine such as 2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT)[4] and 2β-carbomethoxy-3β-(4-fluorophenyl)tropane (β-CFT)[4] have been synthesized from the key synthetic intermediate, anhydroecgonine methyl ester (**3**),[5] which was prepared by the conversion[6] of the natural (1*R*)-cocaine or by the optical resolution[7,4c] of racemic compound **2** (R = Me). Since availability of the natural cocaine is difficult in the market, a new asymmetric synthetic route independent of cocaine has been required for the syntheses of these optically active radiopharmaceuticals. Here we report a novel asymmetric synthesis of 3-oxo-8-azabicyclo-[3.2.1]octane-2-carboxylates (**2**) using porcine liver esterase (PLE)-catalyzed dealkoxycarbonylation of β-keto diesters **1**, and a new route to optically active radiopharmaceuticals such as (1*R*)-β-CIT, as shown in Scheme 1.

Scheme 1. A Novel Asymmetric Dealkoxycarbonylation of Diester **1** and a New Route to (1*R*)-β-CIT



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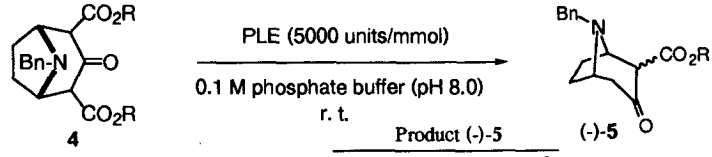
Initially, we examined the lipase-catalyzed demethoxycarbonylation of **1a** (R = Me) with various lipases such as PPL, lipase A, M, AY, PS, and F-AP in a toluene-phosphate buffer, but the obtained **2** (34-48% yields) were completely racemic. Changing the nitrogen substituent from methyl to *t*-butoxycarbonyl (Boc) or benzyloxycarbonyl (Z) resulted in no reaction with the lipases mentioned above or PLE. After searching for a suitable substrate and enzyme, we found that the β–keto diester **4** bearing a benzyl group as an amino-protective group gave optically active β–keto ester **5** with the use of PLE. The results of the dealkoxy-carbonylation of various diesters with PLE are summarized in Table 1. The demethoxycarbonylation of dimethyl ester **4a** with PLE in a phosphate buffer for 24 h gave the monomethyl ester (-)-**5a** in 43% ee (entry 1). The use of an ethyl ester instead of a methyl ester effected a remarkable change in the optical purity of (-)-**5b**. That is, the deethoxycarbonylation of **4b** with PLE gave the monoester (-)-**5b** with 95% ee for 3 h (entry 2). The 24 hours as the reaction time was suitable to give the maximum yield of the product (entry 3). Longer reaction time (48 h) gave lower yield, though it showed the highest enantiomeric excess (97% ee) of (-)-**5b** (entry 4). The high optical purity in entry 4 was assumed to be based on double differentiation in the deethoxycarbonylation of **4b** and **5b** with PLE, because the β–keto ester (-)-**5b** suffered from further deethoxycarbonylation with PLE to give 8-benzyl-3-oxo-8-azabicyclo[3.2.1]octane as the main product. In other alkyl esters **4c-g**, the dealkoxycarbonylation was also tried under the same conditions (entries 5-9). The *n*-butyl ester was the best for giving the highest yield and enantiomeric excess among the ester moieties examined (entry 8).

Table 1. Asymmetric Dealkoxycarbonylation Using Porcine Liver Esterase



4 (-)-5

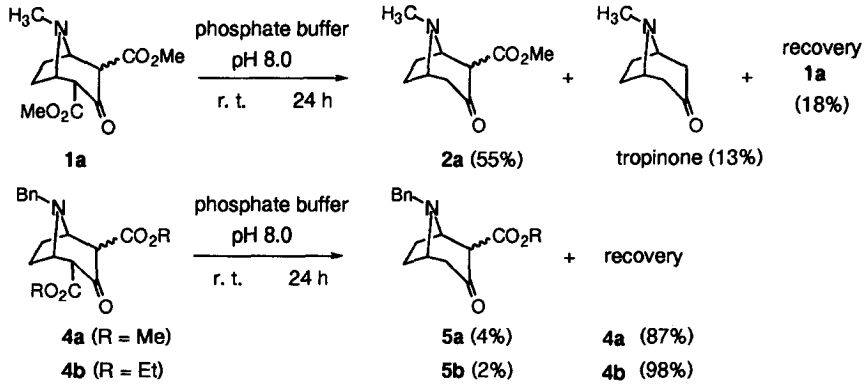
Entry		R	Time (h)	Product (-)-5 yield (%)	Product (-)-5 ee (%) [a]	Recovery of 4 (%)
1	**a**	Me [b]	24	20	43	54
2	**b**	Et	3	30	95	40
3	**b**	Et	24	50	93	21
4	**b**	Et	48	7	97	3 [c]
5	**c**	*i*-Pr	24	15	93	21
6	**d**	Bn	24	51	74	31
7	**e**	*n*-Pr	24	30	93	14
8	**f**	*n*-Bu	24	51	95	17
9	**g**	*n*-Pent	24	29	94	25

a) Enantiomeric excess b) PLE (1000 units/mmol) was used.
c) 8-Benzyl-3-oxo-8-azabicyclo[3.2.1]octane was accompanied in 50 % yield.

Since the enantiomeric excess of the products (-)-**5** could not be directly determined due to the presence of their tautomeric mixture, they were determined by chiral HPLC analyses of α,β–unsaturated methyl ester derived from (-)-**5** using a Daicel CHIRALCEL OD.[8] The absolute configuration of the obtained β-keto esters **5a-g** was estimated from the following experiments: 1) the methyl ester **5a** derived from **5b-g** showed the same (-)-direction in optical rotation, 2) the specific rotation of anhydroecgonine **3** derived from **5f** was identical with that of **3** derived from the known (-)-cocaine, which will be described later in Scheme 3.

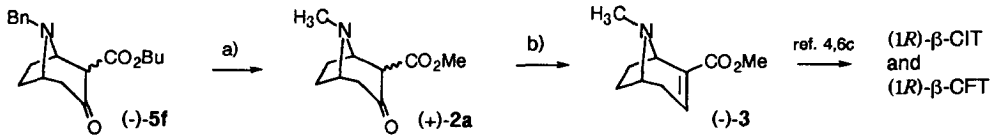
As the result of the above enzymic reactions, it was presumed that the basicity of the substrate is related to their reactivity because the carbamoyl derivatives are unreactive, and the reaction of *N*-methyl derivative **1a** is attributable to nonenzymic dealkoxycarbonylation of the ester moiety in the buffer solution. To elucidate the different reactivity in enzymic dealkoxycarbonylation of β-keto esters depending on the nitrogen substituents (Me and Bn), we tried their hydrolysis in a buffer solution without an enzyme. The nonenzymic demethoxycarbonylation of diester **1a** proceeded in 0.1 M phosphate buffer (pH 8.0) solution to give **2a** (R = Me, 55%), tropinone (13%), and recovered **1a** (18%) at room temperature for 24 h, whereas nonenzymic dealkoxycarbonylation of diesters **4a,b** (R = Me, Et) could be suppressed to only 4% and 2% and **4a,b** was recovered in 87% and 98% yields, respectively, as shown in Scheme 2. We were able to confirm the rapid nonenzymic demethoxycarbonylation of the more basic substrate **1a**, because the order of the amine basicity is *N*-Me > *N*-Bn.

Scheme 2. Nonenzymic Dealkoxycarbonylation of Diesters **1a**, **4a**, and **4b** in Phosphate Buffer



As a synthetic application of the optically active (-)-**5f** (95% ee), we planned the synthesis of radiodiagnostics (1*R*)-β-CIT and (1*R*)-β-CFT, as depicted in Scheme 3. The exchange of the butyl ester to a methyl ester with sodium methoxide, followed by debenzylation of the *N*-benzyl substituent and *N*-methylation by the Clarke-Eschweiler method gave (+)-**2a** in high yield. Reduction of the carbonyl to the alcohol with sodium borohydride and dehydration from the generated alcohol afforded anhydroecgonine methyl ester (-)-**3** in satisfactory yield. The specific rotation {$[\alpha]_D^{21}$ -41.0 (*c* 0.80, MeOH)} of (-)-**3** was consistent with the reported specific rotation {Lit.,[6b] $[\alpha]_D$ -43.0 (*c* 1.50, MeOH)} of the anhydroecgonine methyl ester derived from natural (-)-cocaine;[6] therefore, the absolute structure of keto ester (-)-**5** was clearly determined as shown in Scheme 3.

Scheme 3. Formal Asymmetric Synthesis of (1*R*)-β-CIT and (1*R*)-β-CFT



a) 1) Na, MeOH, 95%, 2) 10% Pd/C, H_2; 3) HCHO, HCO_2H, $(CH_2O)_n$, MeOH, 88% (2 steps),
b) 1) $NaBH_4$ (77%); 2) $POCl_3$ (96%)

In conclusion, we have developed a novel porcine liver esterase (PLE)-catalyzed dealkoxycarbonylation of 3-oxo-8-azabicyclo[3.2.1]octane-2,4-dicarboxylates giving high enantiomeric excess of the desymmetrized keto ester, and also found that the appropriate nitrogen basicity of 3-oxo-8-azabicyclo[3.2.1]octane-2,4-dicarboxylates was an important factor for the novel dealkoxycarbonylation. We were able to provide a new expeditious route to (1*R*)-β-CIT and (1*R*)-β-CFT without the use of cocaine. Further studies are under way to extend the synthetic application of the developed PLE-catalyzed dealkoxycarbonylation.

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