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SYNTHESIS OF COREY LACTONE VIA HIGHLY STEREOSELECTIVE ASYMMETRIC DIELS-ALDER REACTION

Katsuaki Miyaji, Yoshio Ohara, Yasuhiro Takahashi, Toshihiko Tsuruda and Kazutaka Arai*.

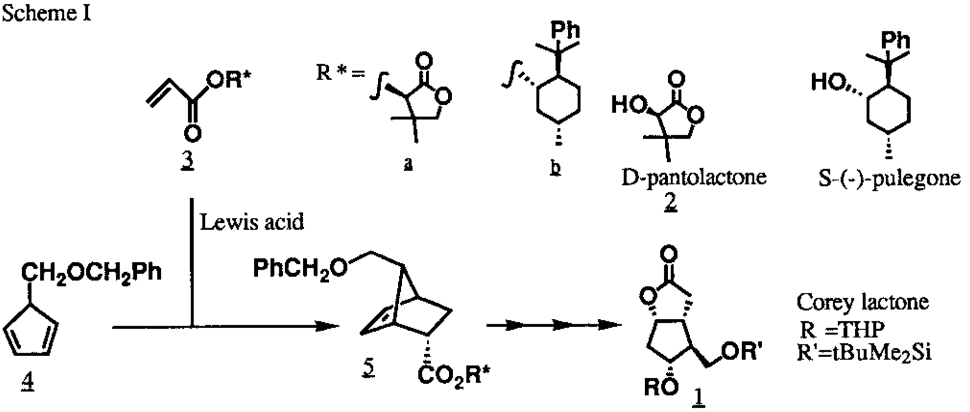
Central Research Institute, Nissan Chemical Ind.Ltd.,
Tsuboi, Funabashi, Chiba 274, Japan

Summary: We have succeeded in a highly stereoselective asymmetric Diels-Alder reaction between a chiral acrylate 3a derived from commercially available D-pantolactone 2 and 5-benzyloxymethyl-cyclopentadiene 4 to give the adduct 5a in 94% d.e. and 79% yield for the synthesis of Corey lactone 1 .

Corey lactone 1 is one of the most important key intermediates in prostaglandin syntheses because of the wide applicability and availability. Many reports about the chiral synthesis of Corey lactone have been known$^{1)}$, and almost *via* optical resolution. In this letter, we wish to report a highly stereoselective asymmetric Diels-Alder reaction and the effective application to the synthesis of Corey lactone 1, providing four asymmetric centers on five-membered ring of 1 at once *via* Diels-Alder reaction.$^{2)}$

There has been only one successful report on the Corey lactone synthesis *via* Diels-Alder reaction by Corey and coworkers themselves$^{3)}$. They also accomplished the high diastereoselectivity in the asymmetric Diels-Alder reaction between 5-benzyloxymethyl-cyclopentadiene 4 and a chiral acrylate 3b. But there have been two drawbacks in the chiral source. Firstly 3b needs four steps to be prepared from S-(-)-pulegone. Secondly S-(-)-pulegone is not commercially available, especially in high optical purity.

Scheme I



So we have searched for the other chiral source, and found D-pantolactone 2 commercially available in high optical purity. And we have also succeeded in a highly stereoselective asymmetric Diels-Alder reaction between a chiral acrylate 3a, prepared from 2 in one step, and 5-benzyloxymethyl-cyclopentadiene 4. The similar Diels-Alder reaction between a chiral acrylate 3a and non-substituted cyclopentadiene have been widely researched by Helmchen et al.4) It is very interesting that even though 4 had a benzyloxymethyl group, which was thought to have a strong interaction with Lewis acids, the high diastereoselectivity could be kept in our reaction.

The dienophile 3a, prepared from D-pantolactone 2 and acryl chloride by one step, was dissolved in methylene chloride and petroleum ether (7:1), and treated with various equivalent of $TiCl_4$ in methylene chloride at -15 °C. To this mixture, was added a methylene chloride solution of 5-benzyloxymethyl-cyclopentadiene 4, prepared from cyclopentadiene according to the reported method 1b). This mixture was maintained for various reaction time at various low temperature and then worked up as usual manner. The chromatographic separation of resultant mixture on silica gel afforded the endo adduct 5a. The results under various reaction conditions are summarized in table 1.

Table 1. Asymmetric Diels-Alder reaction 3a + 4 → 5a***

entry	TiCl4 (eq)*	4 (eq)*	temperature °C (hr)	yield	d.e.
1	0.1	2.5	-60(1.5)	trace	–
2	0.1	2.5	-60(7)→ O.N.**→ 20	50%	92%
3	0.5	2.5	-55(10)→O.N.**→ 0	74%	95%
4	0.5	2.0	-55(4) → -20(16)	79%	94%
5	0.75	2.0	-55(3) → -20(16)	60%	94%

(*equivalent to 3a) (**O.N.=Over night) (***carried out in 5-15 mmol of 3a)

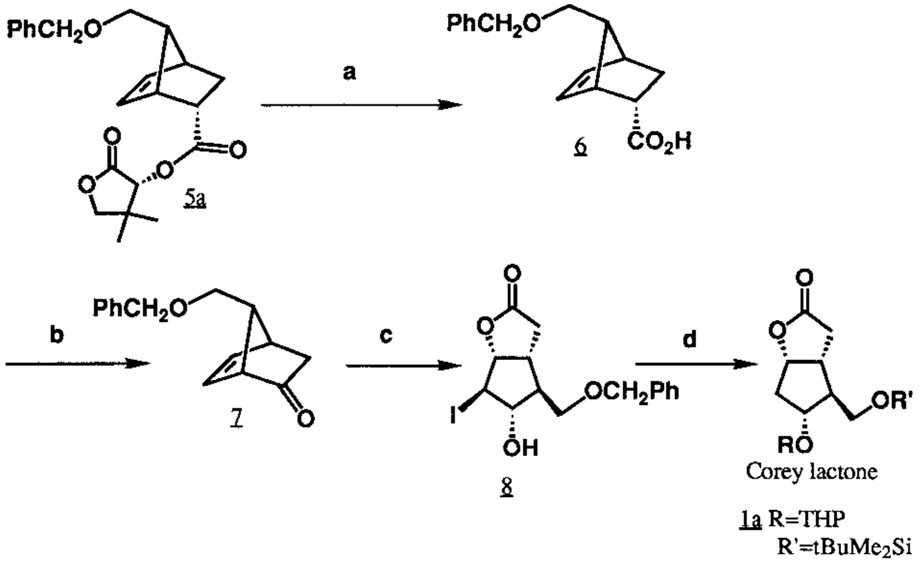
When the reaction temperature was maintained for longer period at low temperature, the yield of 5a showed the tendency to increase. The best amount of $TiCl_4$ was around 0.5 eq to 3a, and less or more amount of the Lewis acid decreased the yield of 5a (entry 2 and 5). We guess these phenomena were due to the essentiality of instability of 3a and 4 under Lewis-acidic condition. The reaction condition of entry 4 gave the highest yield (Y=79%).

The diastereofacial selectivity of this Diels-Alder adduct was determined 94%d.e. by HPLC method5). In addition to this high diastereofacial selectivity, the adduct 5a could be easily purified up to 100%d.e. as colorless crystals (m.p. 96-96.5 °C) by single crystallization in 81%. In a point of view of practical synthesis, this is one of the most distinguished advantages of this reaction.

After hydrolysis of 5a, the resulting carboxylic acid 6 was converted to the ketone 7 and further to the iodolactone 8 according to the reported method6). The iodolactone 8 was obtained in high optical purity ($[\alpha]_D$-34.8°(c=1.0,$CHCl_3$),m.p.120-121 °C)7) Furthermore 8 was actually converted to Corey lactone 1, whose analytical and spectral data are all in complete agreement with authentic sample.

Thus we have succeeded in developing a new synthetic route of Corey lactone 1a, which has included some advantages in practical synthesis.8)

Scheme II



Conditions

a) LiOH (3.8eq) / THF:H_2O=1:1,Y=100%.**b)** 1) LDA (2.5eq) / THF, 2) MeSSMe(1.5eq) 3) NCS(2.0eq) / EtOH, 4) 2N HCl,Y=52%. **c)** 1) H_2O_2(1.5eq)-NaOH(1.3eq) / Et_2O:H_2O= 1:1, 2) KI(3.0eq)-I_2(3.0eq),Y=70%. **d)** 1) DHP(1.5eq),p-TsOH(1mol%) / CH_2Cl_2, 2) Bu_3SnH(1.0eq),AIBN / PhH, 3) H_2,10%Pd-C / EtOH;AcOH=20:1,4)tBuMe_2SiCl(1.1eq), imidazole(1.3eq),Y=78%.

References and Notes

(1) a)E. J. Corey, T. K.Schaaf, W. Huber, U. Koellier and N. M. Weinshenker, J. Am. Chem. Soc., 92, 397 (1970). b)E. J. Corey, H. Shirahama, H. Yamamoto, S. Terasima, A. Venkateswarlu and T. K. Schaaf, J. Am. Chem. Soc., 93,1490 (1971). c)G. Kovacs, I. Szekely and V. Simonidez, Tetrahedron Lett., 50, 4639 (1976). d)J. S. Bindra, A. Grodski and T. K. Schaaf, J. Am. Chem. Soc., 95, 7522 (1973).

(2) Review for asymmetric Diels-Alder reaction. W. Oppolzer, Angew. Chem. Int. Ed. Engl., 23, 876 (1984).

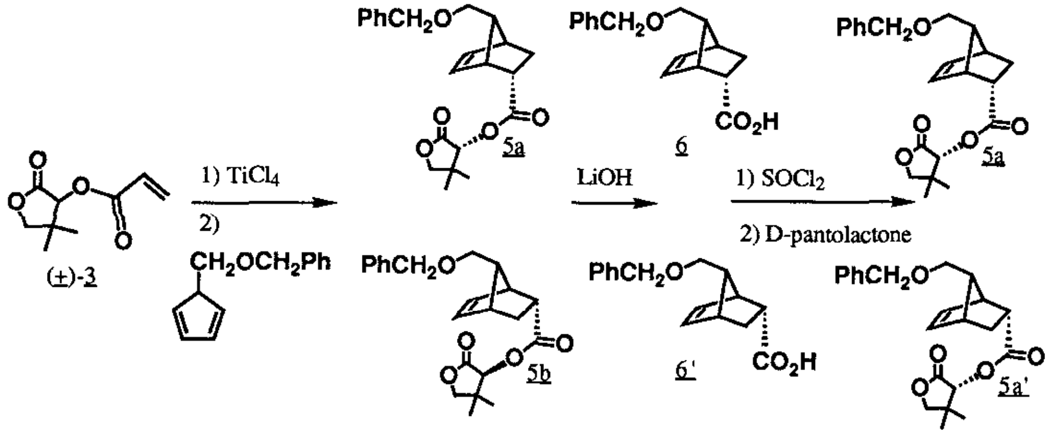
(3) E. J. Corey and H. E. Ensley, J. Am. Chem. Soc., 97, 6908 (1975).

(4) T. Poll, A. Sobczak, H. Hartmann and G. Helmchen, Tetrahedron Lett., 26, 3095 (1985).

(5) HPLC analysis (column; YMC-PACK A-303 ODS, eluent; MeOH:H_2O =4:1, flow rate; 1ml / min, 254 n.m.).

The chromatogram showed two peaks with t_R= 6.4 min and t_R= 6.8 min in 97:3 ratio assignable to desired compound 5a and its diastereomer 5a' respectively.

We prepared the authentic sample of 1:1 mixture of 5a and 5a' in the following route.



(6) B. M. Trost and Y. Tamaru, J. Am. Chem. Soc., 97, 3528 (1975).

(7) $[\alpha]_D$ -34.0° (c=1.1, $CHCl_3$): prepared by resolution of precursor unsaturated acid as the (+)-amphetamine salt 1b) and $[\alpha]_D$ -33.3° (c=1.3, $CHCl_3$):prepared by asymmetric Diels-Alder reaction. 3)

(8) K. Miyaji, K. Arai, Y. Ohara and Y. Takahashi, USP 4,837,344 (1989).

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