Asymmetric Synthesis of 5- and 6-Membered Lactones from Cyclic Substrates Bearing a C_2-Chiral Auxiliary[1]

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Optically active lactones were synthesized by a novel asymmetric synthesis in which enantiotopic groups remote from a prochiral center were effectively discriminated. The cyclic diamide alcohols bearing a C_2-chiral auxiliary, (+)-[1,1'-binaphthyl]-2,2'-diamine (**4**), were designed and prepared such that the hydroxyl group should attack preferentially at one of the two carbonyl groups. By the catalytic action of trifluoroacetic acid, the substrates **6a,b** and **19** were smoothly converted to the lactones **7a** (71% de), **7b** (97% de), and **20** (>99% de), the configurations of which were determined to be *R*, *S*, and *R*, respectively. A naturally occurring pheromone, (*R*)-(+)-5-hexadecanolide (**13**), was synthesized optically pure from **7b**. Transition-state models for the present asymmetric lactonization were constructed according to the stereoelectronic theory proposed by Deslongchamps. The stability of the models was assessed by MM2 calculation, and the direction of asymmetric induction thus calculated coincided with the experimental results.

Asymmetric induction based on the differentiation between enantiotopic groups in prochiral and *meso* molecules has been recognized as an efficient strategy for the preparation of optically active compounds.[2] Enzymatic hydrolysis, esterification, and oxidation of prochiral substrates belonging to this category have been widely employed for syntheses of chiral building blocks of natural products.[3] This process has, however, the disadvantage that asymmetric yields are substantially lowered by the intervention of methylene groups between the prochiral center and the ester group.[4] Should the functional group at the prochiral center be designed so as to participate in the reaction, the intramolecular asymmetric synthesis would be expected to exhibit a higher level of selectivity. On the basis of this rationale, we undertook the development of new methodology for asymmetric lactonization. We have designed and prepared the cyclic compounds containing a C_2-chiral auxiliary in the ring structure constrained so as to allow the hydroxyl group to attack preferentially either the *pro-S* or *pro-R* carbonyl group of the substrate. In accord with this expectation, high selectivity in the lactonization was observed as described below.

Asymmetric Lactonization. Diacids **2a** (n = 2) and **2b** (n = 3) were prepared from the known keto diacids **1a**[5] and **1b**[6] according to Scheme I. The condensation of the diacid chlorides **3a,b** derived from **2a,b** and (*R*)-(+)-[1,1'-binaphthyl]-2,2'-diamine (**4**)[7] under high-dilution conditions gave the key intermediates **5a** (39%) and **5b** (56%). Alkaline hydrolysis of **5a,b** afforded the hydroxyl derivatives **6a,b**.[8]

First, asymmetric synthesis of the 5-membered lactone **7a** from **6a** (n = 2, R = H) was examined. For purposes of reference in the assessment of the de of the desired product **7a** from the asymmetric reaction, an authentic sample of **7a** bearing the racemic lactone moiety was independently prepared from (±)-lactone acid **9a**[9] and (+)-**4**. The diastereomers of **7a** proved to be completely separable by HPLC under the conditions described in Table I. The de was also confirmed by ^{1}H NMR (200 MHz) spectroscopy monitoring of the methine proton H_a; δ 3.90–4.09 for the *R* isomer and 4.27–4.43 for the *S* isomer.

After examining several inorganic and organic acids, including Lewis acids, as lactonization catalysts, we found trifluoroacetic acid (TFA) to be the most effective. When a solution of **6a** was treated with TFA in toluene or dichloromethane, the 5-membered lactone derivative **7a** was obtained (Table I). The reaction conversions and the de's of **7a** were determined by HPLC analysis. In order to

(1) A preliminary communication on this subject has appeared: Sakamoto, A.; Yamamoto, Y.; Oda, J. *J. Am. Chem. Soc.* **1987**, *109*, 7188.

(2) The relevant articles have been cited in ref 1. The followings are more recent developments: (a) Inagaki, M.; Hiratake, J.; Yamamoto, Y.; Oda, J. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121. (b) Hiratake, J.; Shibata, K.; Baba, N.; Oda, J. *Synthesis* **1988**, 278. (c) Nagao, Y.; Hagiwara, Y.; Hasegawa, Y.; Ochiai, M.; Inoue, T.; Shiro, M.; Fujita, E. *Chem. Lett.* **1988**, 381. (d) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374. (e) Aitken, R. A.; Gopal, J.; Hirst, J. A. *J. Chem. Soc., Chem. Commun.* **1988**, 632. (f) Niwa, H.; Okamoto, O.; Yamada, K. *Tetrahedron Lett.* **1988**, *29*, 5139. (g) Duhamel, L.; Ravard, A.; Plaquevent, J.-C.; Dovoust, D. *Ibid.* **1987**, *28*, 5517. (h) Asami, M.; Kirihara, H. *Chem. Lett.* **1987**, 389. (i) Yamashita, H. *Ibid.* **1987**, 525. (j) Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527.

(3) For recent examples, see: (a) Yamamoto, K.; Nishioka, T.; Oda, J.; Yamamoto, Y. *Tetrahedron Lett.* **1988**, *29*, 1717. (b) Yamamoto, Y.; Yamamoto, K.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1988**, *52*, 3087. (c) Taschner, M. J.; Black, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 6892. (d) Terao, Y.; Murata, M.; Achiwa, K.; Nishio, T.; Akamatu, M.; Kamimura, M. *Tetrahedron Lett.* **1988**, *29*, 5173. (e) Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3127. (f) Hemmerle, H.; Gais, H.-J. *Tetrahedron Lett.* **1987**, *28*, 3471. (g) Theil, F.; Ballschuh, S.; Schick, H.; Haupt, M.; Hafner, B.; Schwarz, S. *Synthesis* **1988**, 540. For reviews, see: (h) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351. (i) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695.

(4) (a) Mohr, P.; Sarcevic, N. W.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 2501. (b) Recently, enzymatic lactonization of a similar substrate was reported to proceed with high enantioselectivity: Gutman, A. L.; Bravdo, T. *J. Org. Chem.* **1989**, *54*, 4263.

(5) Emerson, W. S.; Longley, R. I., Jr. *Organic Syntheses*; Wiley: New York, 1946; Collect. Vol. 4, p 302.

(6) Durham, L. J.; McLeod, D. J.; Cason, J. *Organic Syntheses*; Wiley: New York, 1946; Collect. Vol. 4, p 555.

(7) Brown, K. J.; Berry, M. S.; Murdoch, J. R. *J. Org. Chem.* **1985**, *50*, 4345.

(8) ^{13}C NMR spectra of **6a** as well as **19** at 25 °C showed very broad signals. When the measurement was carried out at −40 °C, the signals separated into several complicated peaks. Consequently, **6a** and **19** were considered to exist as conformers whose interconversion was relatively slow.

(9) Racemic lactone acid **9a** was prepared by alkaline hydrolysis of diisopropyl 4-hydroxyheptanedioate followed by lactonization under acidic conditions. After converting to the acid chloride, (±)-**9a** was coupled with (+)-**4** to give the diastereomeric mixture of **7a**. By a similar reaction sequence, the diastereomeric mixtures of **7b** and **20** were also obtained as the reference compounds for the NMR experiment.

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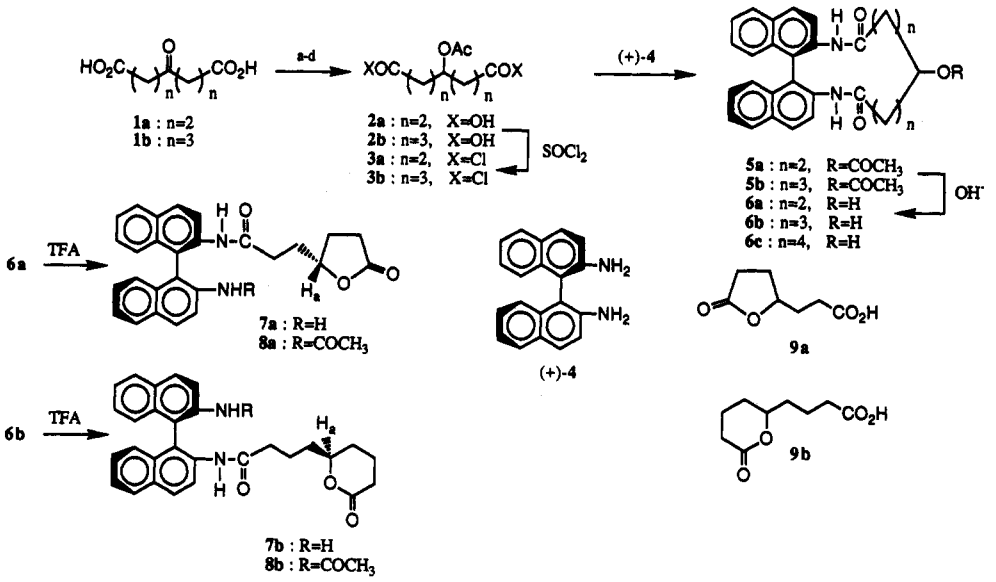
Scheme I[a]



[a] (a) 2-Methylpropene/H^+; (b) $NaBH_4$; (c) $(CH_3CO)_2O$/pyridine; (d) HCO_2H.

Table I. Lactonization of Cyclic Diamide Alcohols 6a,b to 5- and 6-Membered Lactones 7a,b

	substrate						product	
entry	compd	concn (mg/mL)	concn of TFA (% v/v)	solvent	reaction temp (°C)	convn (%)[b]	compd	% de
1[a]	**6a**	1	0.5	toluene	−40	75	**7a**	67[b]
2	**6a**	1	0.5	toluene	−20	100	**7a**	71[b]
3	**6a**	1	0.5	toluene	25	96	**7a**	63[b]
4	**6a**	4	0.5	toluene	−20	100	**7a**	69[b]
5	**6a**	1	5.0	toluene	−20	88	**7a**	53[b]
6	**6a**	1	0.5	CH_2Cl_2	−20	99	**7a**	46[b]
7	**6a**	1	0.5	THF	−20	18	**7a**	66[b]
8	**6b**	1	0.5	toluene	−20	98	**7b**	>83[c]
9	**6b**	1	0.5	CH_2Cl_2	−20	98	**7b**	>85[c]
10	**6b**	1	2.0	CH_2Cl_2	−20	98	**7b**	>88[c]
11	**6b**	5	2.0	CH_2Cl_2	−20	98	**7b**	>87[c]

[a] Typical procedure: To a solution of **6a** (2 mg) in toluene (1 mL) was added a 1% (v/v) solution (1 mL) of TFA in toluene at −40 °C. The mixture was stirred at −40 °C for 15 h. After the mixture was neutralized with pyridine, an aliquot of the mixture was analyzed by HPLC. [b] Determined by HPLC: retention time (*R*-**7a**) 12 min; retention time (*S*-**7a**) 14 min. [c] Determined by ^1H NMR analysis (200 MHz). Because the peaks overlap partly, the lowest values calculated from the peak areas are presented.

optimize stereoselectivity as well as reaction conversion, the concentrations of **6a** and TFA were changed at various reaction temperatures. When **6a** reacted under the condition of entry 2, **7a** having a maximum de of 71% was obtained in 92% yield. On the other hand, this reaction was much retarded in THF (entry 7) and did not proceed at all in ethanol. In dichloromethane, **7a** with 46% de was formed almost quantitatively (entry 6). When a THF solution of **6a** was treated with 6 N hydrochloric acid, **7a** was obtained in 84% yield and 53% de.

The absolute configuration of **7a** was determined by converting it to the known lactone alcohol **11a** (Scheme II). Starting from **7a** of 47% de, acetylation with acetic anhydride followed by reduction with lithium borohydride gave the diol **10a**. When **10a** was treated with hydrochloric acid, **11a** having $[\alpha]^{25}_D$ −24.2° was obtained. Consequently, the *R* configuration of the lactone moiety of **7a** was proven based on the established *S* configuration of (−)-**11a**.[10a] It should be noted that the inversion of configuration is ascribed to carboxyl interchange during the synthetic sequence. This result indicates that the hydroxyl group on the ring attacked preferentially on the *pro-R* carbonyl group of **6a** (n = 2, R = H). Since different values of the maximum rotation of **11a** have been reported,[10] we independently determined the ee of **11a**. After protecting the hydroxyl group, **11a** was converted to diol **12** with methyllithium. According to Jones' procedure,[11] **12** was assigned the 47% ee by ^1H NMR analysis using a chiral shift reagent. This value agrees well with the de of **7a** used in this experiment.

As to the cyclic diamide alcohol **6b** (n = 3, R = H), optimization of the reaction conditions was carried out as with **6a** (n = 2, R = H). Based on the results of **6a**, a limited variation of conditions was examined for **6b**, under which the reaction proceeded almost quantitatively (Table I). The diastereomeric mixture of **7b** also prepared from (+)-4 and (±)-**9b**[9] was not separable by HPLC. However, the de's of **7b** were successfully estimated by ^1H NMR (200 MHz) analysis of the lactone methine proton H_a. Because these signals overlapped partially, the de's in Table I merely indicate the minimum values calculated from the NMR experiment. In contrast to the 5-membered counterpart **7a**, the de's of the 6-membered lactone **7b** were almost the same in toluene or dichloromethane.

(10) (a) Fuji, K.; Node, M.; Terada, S.; Murata, M.; Nagasawa, H. *J. Am. Chem. Soc.* **1985**, *107*, 6404. (b) Pirillo, D.; Leggeri, P.; Vercesi, D.; Azzolina, O.; Traverso, G. *Farmaco, Ed. Sci.* **1985**, *40*, 623; *Chem. Abstr.* **1986**, *104*, 5716p.

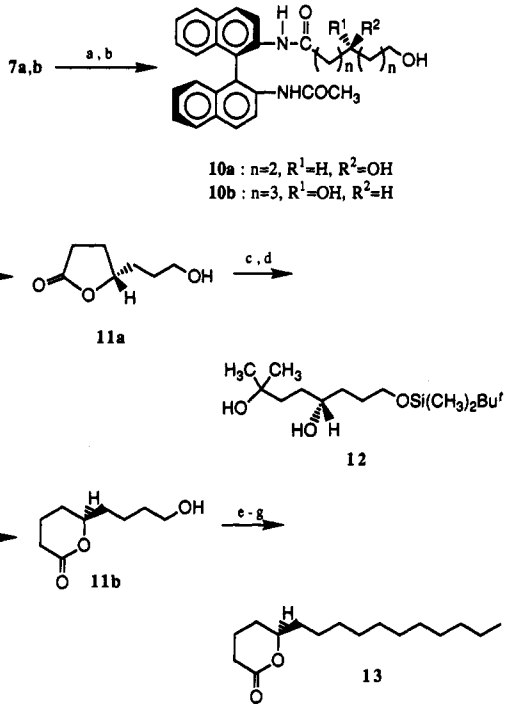
(11) Jakovac, I.; Jones, J. B. *J. Org. Chem.* **1979**, *44*, 2165.

Table II. Lactonization of Linear Diamide Alcohols 14a,b and 15a,b to 7a,b and 8a,b[a]

	substrate				product		
entry	compd	n	R	convn (%)[b]	compd	% de	config
1	**14a**	2	H	85	**7a**	20[b]	*S*
2	**14b**	3	H	100	**7b**	44[c]	*S*
3	**15a**	2	$COCH_3$	100	**8a**	15[d]	*R*
4	**15b**	3	$COCH_3$	100	**8b**	57[e]	*R*

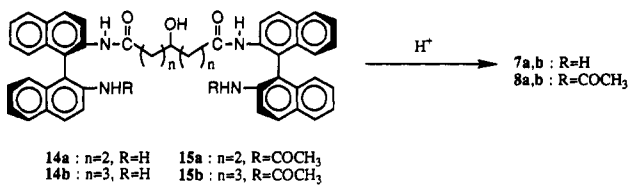
[a] The reaction conditions were the same as those described below Table I except that the temperature was maintained at 25 °C. [b] Determined by HPLC. [c] Determined by ^1H NMR (200 MHz). [d] Determined by ^1H NMR (200 MHz); the lactone methine protons of the *R* and *S* isomers appeared at δ 3.92–4.08 and at δ 4.08–4.25, respectively. [e] Determined by converting **8b** to **11b** having $[\alpha]^{25}_D$ −29.1° (*c* 1.18, EtOH): the maximum rotation of **11b** was calculated to be 51.0° in the prior section.

Scheme II[a]



[a] (a) $(CH_3CO)_2O/Et_3N$; (b) $LiBH_4$; (c) $Bu^t(CH_3)_2SiCl/Et_3N$; (d) CH_3Li; (e) DMSO, $(COCl)_2$, Et_3N; (f) $C_7H_{15}(C_6H_5)_3PBr$, Bu^tOK; (g) H_2/Pd–C.

Scheme III



When **6b** reacted under the conditions of entry 11, **7b** was obtained in a yield of 88%. Base-line separation of H_a signals was attained in the ^1H NMR spectra (400 MHz): δ 3.92–4.00 for the *R* isomer and 4.07–4.16 for the *S* isomer. Based on this analysis, the de of **7b** was determined to be 97%.

When **6b** was treated with aqueous hydrochloric acid, the racemic lactone carboxylic acid **9b** was obtained in 36% yield along with a trace amount of the desired 6-membered lactone derivative **7b**.

In order to establish the absolute configuration of **7b**, it was converted to lactone alcohol **11b** by the same procedure used for **7a**, except that **10b** was treated with *p*-toluenesulfonic acid in dichloromethane. The *R* configuration of **11b** was established by converting it to the naturally occurring pheromone[12] (*R*)-(+)-hexadecanolide (**13**)[13] by successive Swern oxidation, Wittig reaction, and hydrogenation (Scheme II). Consequently, the *S* configuration is assigned to the lactone moiety of **7b**. This result indicates that the *pro-S* carbonyl group of **6b** (n = 3, R = H) was preferentially attacked intramolecularly by the hydroxyl group. The ee of (+)-**13** thus obtained ($[\alpha]^{20}_D$ +39.97°.[12] An optically pure sample was obtained by recrystallization from hexane, $[\alpha]^{20}_D$ +39.81°. Accordingly, this reaction sequence provides an efficient synthesis of the natural pheromone (+)-**13**.

The homologue (**6c**, n = 4) of **6a,b** which should give a 7-membered lactone was also synthesized. However, this compound gave the trifluoroacetyl ester along with a trace amount of the lactone under the same conditions for the reaction of **6a,b**. The yield of the desired lactone was also very low when *p*-toluenesulfonic acid or (+)-10-camphorsulfonic acid were employed as the catalyst.

Besides the cyclic substrates **6a,b**, we prepared the linear diamide alcohols **14a,b** and **15a,b**.[14] The amino groups on the naphthyl rings of **15a,b** were protected with acetyl groups. They have two binaphthyl units as the chiral auxiliaries, and the two carbonyl groups are diastereotopic with each other.

When **14a,b** and **15a,b** were treated with a solution of TFA in dichloromethane at 25 °C, the 5-membered lactone derivatives **7a** and **8a** and the 6-membered lactone derivatives **7b** and **8b** were produced, respectively (Scheme III, Table II). Since the de's of the products were not as high as those of the cyclic substrates, we examined other acid catalysts, e.g. *p*-toluenesulfonic acid and 10-camphorsulfonic acid, and other solvents at lower temperature. However, the de's of the products were not improved. These results indicate that the high selectivity of the present asymmetric synthesis of **7a,b** can be ascribed to the cyclic structure of **6a,b** as well as the design that the hydroxyl group at the prochiral center attacks directly on the enantiotopic carbonyl groups.

Because the present acid-catalyzed reaction yielded effectively both 5- and 6-membered lactones, we examined other substrates which should afford lactones having the same ring sizes. Replacing the hydroxyl group of **6a** (n = 2) by a hydroxymethyl group, a new substrate for the present asymmetric synthesis was generated which should give a 6-membered lactone derivative. At first sight, insertion of a methylene group between the prochiral center and the hydroxyl group might reduce the stereoselectivity.

Cyclic diamide alcohol **19** was prepared according to Scheme IV. Diester **16** was obtained from the keto diacid **1a** (n = 2) through successive Wittig reaction and hydroboration. Condensation of the diacid chloride **17** derived

(12) Ikan, R.; Gottlieb, R.; Bergmann, E. D.; Ishay, J. *J. Insect Physiol.* **1969**, *15*, 1709.

(13) (a) Servi, S. *Tetrahedon Lett.* **1983**, *24*, 2023. (b) Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. *Ibid.* **1985**, *26*, 771.

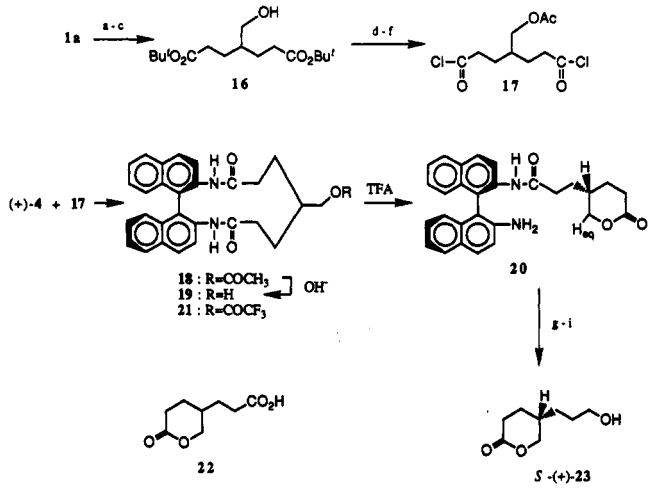
(14) Linear substrates **14a,b** were prepared from **3a,b**, respectively, by a similar manner to the cyclic analogues **6a,b** without using the high-dilution technique.

Table III. Lactonization of Cyclic Diamide Alcohol 19 to 6-Membered Lactone Derivative 20[a]

entry	concn of TFA (% v/v)	reaction temp (°C)	reaction period (h)	convn (%)[b]	TFA ester 21 (%)[b]	de of 18[c]
1	0.5	−20	24	93	27	>99
2	0.5	+20	1	89	13	>99
3	0.1	+40	0.5	99	0	>99

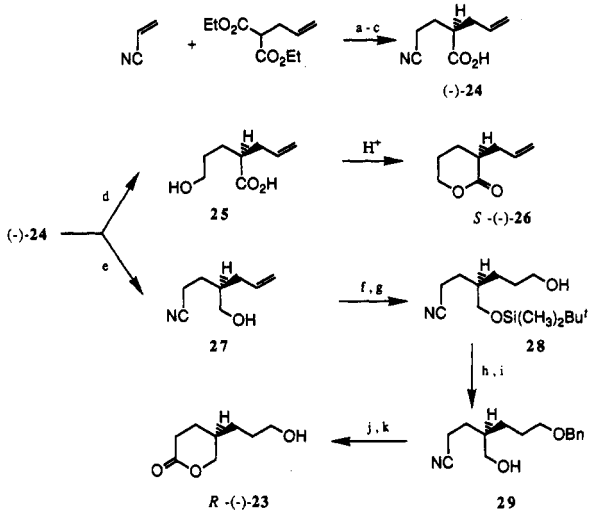
[a] The reaction conditions were the same as those described in Table I except that dichloromethane was used as solvent. [b] Determined by HPLC. [c] Determined by ^{1}H NMR (400 MHz).

Scheme IV[a]



[a] (a) 2-Methylpropene/H$^+$; (b) $CH_3(C_6H_5)_3PBr$, Bu^{t}OK; (c) 9-BBN, H_2O_2, NaOH; (d) $(CH_3CO)_2O$/pyridine; (e) HCO_2H; (f) $SOCl_2$; (g) $(CH_3CO)_2O/Et_3N$; (h) $LiBH_4$; (i) *p*-toluenesulfonic acid.

Scheme V[a]



[a] (a) Bu^{t}OK; (b) KOH then heating; (c) (−)-$C_6H_5CH(NH_2)CH_3$; (d) DIBAL-H then $NaBH_4$; (e) CH_2N_2 then $LiBH_4$; (f) Bu$^t(CH_3)_2$SiCl/imidazole; (g) 9-BBN, H_2O_2, NaOH; (h) $C_6H_5CH_2Br$, Bu^{t}OK; (i) H_2SO_4; (j) KOH then H$^+$; (k) $H_2/Pd(OH)_2$.

from **16** and (+)-**4** gave **18** in 42% yield which was converted to **19**[8] by alkaline hydrolysis.

At first, **19** was treated with TFA under conditions similar to those for the reaction of **6a,b** and a high de of **20** was observed. However, a significant amount of the trifluoroacetate **21** was formed (entry 1, Table III). To suppress ester formation, the concentration of TFA was lowered, and the reaction temperature was elevated. As was expected, the lower concentration of TFA resulted in reduced formation of **21** and, fortunately, elevating the temperature did not affect the de of **20**.

When **19** was reacted under the conditions of entry 3 in Table III on a preparative scale, **20** was obtained in 78% yield. Lactone amide **20** thus obtained exhibited only one signal in the ^{1}H NMR spectrum (δ 3.95–4.02, 400 MHz) corresponding to H_{eq} (the equatorial proton adjacent to oxygen). On the other hand, a pair of signals (δ 3.95–4.02 and 4.04–4.12) was observed in the spectrum of **20** derived from (+)-**4** and the racemic lactone acid **22**.[9] Accordingly, the product **20** of this asymmetric reaction could be concluded to have an ee above 99% in consideration of the S/N of the spectrum.

The chiral auxiliary was removed to give lactone alcohol (+)-**23** in a manner similar to the other lactone amides: successive N-acetylation, reduction of the lactone moiety to the diol, and lactonization with *p*-toluenesulfonic acid. Since no compound with known absolute configuration was found which could be directly derived from **23**, we correlated its configuration indirectly. That is, the key compound (−)-**24** prepared from acrylonitrile and diethyl allylmalonate was optically resolved with (−)-α-methylbenzylamine. According to Scheme V, (−)-**24** was converted to **23** as well as 2-allyl-5-pentanolide (**26**) whose configuration had already been established.[15]

At first, the nitrile group of (−)-**24** was selectively reduced successively with diisobutylaluminum hydride (DIBAL-H) and sodium borohydride to give hydroxy acid **25**, which was then cyclized to *S*-(−)-**26**.[15] On the other hand, the carboxyl group of (−)-**24** was esterified and then reduced with lithium borohydride to give the hydroxy nitrile **27**. After six steps of reactions, **27** was converted to (−)-**23** through **28** and **29**. No reaction which jeopardized the configuration of the chiral center was involved in this transformation. Consequently, the *R* configuration is assigned to (−)-**23** based on *S*-(−)-**26**. Because *S*-(+)-**23** was obtained from **20** (Scheme IV), it follows that the configuration of the lactone moiety of **20** was determined to be *R*. This conclusion implies that the *pro-R* carbonyl group of **19** was preferentially attacked.

In conclusion, the present asymmetric synthesis was applied to **6b** and **19** to provide the 6-membered lactone products of high selectivity. Although lower selectivity was observed with **6a**, we have recently reported elsewhere[16] that the same 5-membered lactone (96% de) was obtained by the use of (*R,R*)-1,2-diphenylethylenediamine as a chiral auxiliary.

Calculations for Intermediate Models. Although high selectivity was attained in the above asymmetric synthesis, the reason is still obscure why **6b** afforded the *S* lactone while **6a** and **19** having the same chiral auxiliary yielded the *R* lactones. It is impossible to ascribe the phenomenon to a single factor considering steric effects visualized by the use of a molecular model. It should be rationalized in terms of the difference in integrated conformational energies of the transition states leading to each

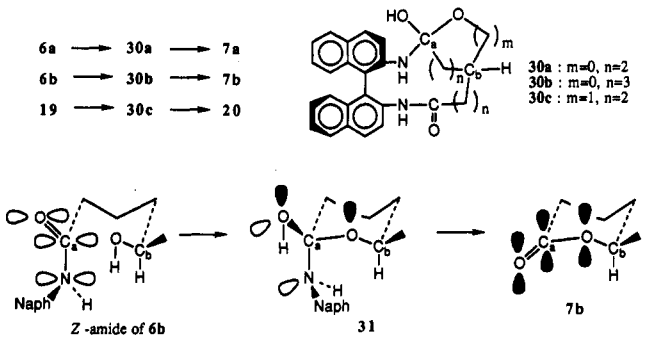
(15) Meyers, A. I.; Yamamoto, Y.; Mihelich, E. D.; Bell, R. A. *J. Org. Chem.* **1980**, *45*, 2792.

(16) Baba, N.; Sakamoto, A.; Mimura, M.; Yamamoto, Y.; Uchida, K.; Oda, J. *Chem. Lett.* **1989**, 889.

Table IV. Stereoselectivity of Lactonization Found Experimentally and Estimated by MM2 Calculation

reaction		config of product		energy difference (kcal/mol)	
subst	product	found	calcd	found	calcd
6a	7a	R	R	0.89 (71% de)	3.75
6b	7b	S	S	2.10 (97% de)	4.53
19	20	R	R	>3.3 (>99% de)	8.47

Scheme VI



diastereomer. In this context, we tried to estimate the energy differences by the molecular mechanics method.

We first assumed that the energy differences of the transition states could be approximated by the conformational energy differences between the diastereomeric tetrahedral intermediates **30**, arising from cyclization of the hydroxyl group to one of the two carbonyl group (Scheme VI). These intermediates should have configurations consistent with the stereoelectronic effects proposed by Deslongchamps.[17] In order to permit appropriate orientation of orbital lobes on nitrogen and oxygen atoms required by this theory, the nitrogen atom attached to C_a should occupy an axial position as shown in **31**. Orientations of the hydrogen atoms on oxygen and nitrogen as well as the naphthyl group on nitrogen are also restricted. For each substrate, two pathways exist leading to the *R* and the *S* lactones, respectively, which relates to the configuration of C_b. In addition to this chiral center which remains in the product, temporary chiralities should be also considered. That is, the tetrahedral reaction center C_a is also chiral but disappears in the product. Moreover, two coordinates can be constructed for each intermediate which are derived from the *Z* and the *E* orientation of the substrate amide. This fact relates to the configuration of nitrogen in **30**. Consequently, each intermediate has three chiral centers, and eight models are constructed according to the configurations of product (C_b), reaction center (C_a), and nitrogen atom (or conformation of amide in substrate). As an example, one of the eight coordinates of **30b** is illustrated in **31** which is generated from the *Z*-amide.

The conformational energies of the postulated intermediates were assessed by MM2 calculation.[18] Because this molecular mechanics program is not fully parametarized for the molecules under study, ad hoc parameters around the nitrogen atom were estimated by use of MNDO calculations.[19] By the use of a program (MMRS) developed by one of the authors.[20] the initial coordinates were constructed fixing the orientation around C_a and varying other parts of the molecules.[21] In order to avoid deviation from the Deslongchamps type orientation around C_a during energy minimizing process, dihedral angels of O(ring)–C–N–C(naph) and O(ring)–C–O–H were fixed in the calculation.

The results of these calculations are summarized in Table IV and coincide with the experiments in trend of selectivity. The experimental results and the calculations coincide totally as to the product configurations. Although the magnitudes of energy differences between *R* and *S* lactonization are not reproduced well by the present calculation, the calculated values are larger than the observed ones in all the cases.[22] It is noteworthy that the order of magnitudes of the asymmetric induction in the experiment agrees well with that obtained by the calculation.

Experimental Section

General Procedure. Boiling points and melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$. HPLC analyses were done on a silica gel column (NUCLEOSIL 50-5, 4 mm × 25 cm; eluant, hexane–2-propanol–triethylamine, 63:35:2, 1.0 mL/min) and a UV detector (280 nm). Reactions were run in oven-dried glassware, and anhydrous reagents were transferred by dried syringes. Toluene and CH_2Cl_2 used as solvents for the cyclization, and the lactonization reaction were distilled over P_2O_5. Cyclization reactions were performed under high-dilution conditions using a Micro Feeder (Furue Science Co. Ltd., Japan). The products were isolated by bulb-to-bulb distillation on a Büchi Kugelrohr apparatus or flash column chromatography on silica gel (Kieselgel 60, 230–400 mesh, E. Merck Co. Ltd.).

(*R*)-(+)-[1,1′-Binaphthyl]-2,2′-diamine (4). A mixture of 2-naphthol (80 g, 0.55 mol) and 80% $NH_2NH_2{\cdot}H_2O$ (18 mL, 0.29 mol) in a glass cylinder was set in an autoclave and was heated between 170 and 180 °C for 48 h. After cooling, a gummy mass obtained was triturated mechanically with 50% EtOAc in hexane (70 mL) upon which the product crystallized out while the byproducts were dissolved. The crystals were decanted with the solution. This treatment was repeated (3 times) until the gummy mass disappeared. Diamine **4** was collected by filtration (30 g, 38%). Optical resolution was effected with (+)-camphor-10-sulfonic acid according to the literature:[7] $[\alpha]^{25}_D$ +149.7° (*c* 1.487, pyridine) [lit.[7] $[\alpha]^{20}_D$ +149.5° (*c* 1.482, pyridine)].

4-Acetoxyheptanedioyl dichloride (3a) was prepared by the same reaction sequence described below for **3b**. The yields of the intermediary products were as follows: di-*tert*-butyl 4-oxoheptanedioate, 79% (a reaction period of 7 days); di-*tert*-butyl 4-hydroxyheptanedioate, 93%; di-*tert*-butyl 4-acetoxyheptanedioate, 83%; 4-acetoxyheptanedioic acid (**2a**), 100%. The dichloride **3a** (95%): ^1H NMR (60 MHz) δ 1.8–2.2 (m, 4 H), 2.10 (s, 3 H), 2.95 (t, *J* = 7.0 Hz, 4 H), 4.7–5.2 (m, 1 H).

5-Acetoxynonanedioyl Dichloride (3b). 5-Oxononanedioic acid (**1b**) was prepared in 44% yield from glutaric anhydride according to the procedure for the homologue.[6] Diacid **1b** (2.72 g, 13.5 mmol) was added to a mixture of 2-methylpropene (3.77 g, 67.3 mmol), concentrated H_2SO_4 (0.16 mL), and anhydrous tetrahydrofuran (THF, 1.6 mL). The mixture was stirred in a

(17) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Organic Chemistry Series; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1983; Vol. 1, p 101.

(18) Allinger, N. L. *J. Am. Chem. soc.* **1977**, *99*, 8127; *QCPE* **1977**, *No 395*.

(19) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907.

(20) Fukazawa, Y.; Usui, S.; Uchio, Y.; Shiobara, Y.; Kodama, M. *Tetrahedron Lett.* **1986**, *27*, 1825.

(21) Since **30** has a flexible large-membered ring (**30a**, **30c**, 13-membered; **30b**, 15-membered), the most stable conformer having a fixed orientation around C_a was selected from all possible conformers generated by our MMRS program[20] (ring closure program utilizing tree search type algorithm).

(22) According to the Bell[23] and the Evans and Polanyi[24] principle, it is normal that the energy difference of the products (or intermediates) is larger than that of the transition states.

(23) Bell, R. P. *Proc. R. Soc. London, Ser. A* **1936**, *154*, 414.

(24) (a) Evans, M. G.; Polanyi, M. *J. Chem. Soc., Faraday Trans.* **1936**, *32*, 1340. (b) Klumpp, G. W. *Reactivity in Organic Chemistry*; John Wiley & Sons: New York, 1982; p 328.

sealed tube at room temperature for 4 days and then poured into a ice-cooled solution (50 mL) of NaOH (2.2 g). The oil liberated was extracted 3 times with ether, and the combined extracts were dried (K_2CO_3). Evaporation gave di-*tert*-butyl 5-oxononanedioate (2.39 g, 57%).

This oxo diester (2.10 g, 6.69 mmol) was reduced with $NaBH_4$ (0.253 g, 6.69 mmol) in EtOH (60 mL) at 0 °C for 10 min. After stirring for further a 20 min at room temperature, the mixture was evaporated and diluted with ether (50 mL). The solution was washed with water and dried ($MgSO_4$). Evaporation gave di-*tert*-butyl 5-hydroxynonanedioate (2.04 g, 97%).

This alcohol (2.15 g, 6.79 mmol) was acetylated with acetic anhydride (3.5 g, 34 mmol) and pyridine (5.5 mL) at room temperature for 15 h. The mixture was evaporated, and the residue was treated with 90% formic acid (10 mL) at room temperature for 15 h, and the mixture was evaporated to give **2b**. After coevaporating with toluene, the residue was treated with thionyl chloride (2 mL) at room temperature for 2 h. Evaporation gave **3b** as an oil (1.61 g, 84%): ^{1}H NMR (200 MHz) δ 1.55–1.85 (m, 8 H), 2.07 (s, 3 H), 2.95 (t, J = 6.0 Hz, 4 H), 4.84–4.98 (m, 1 H).

Cyclic *O*-acetyl derivative 5a (n = 2) was prepared from the dichloride **3a** (1.29 g, 5.06 mmol) according to the procedure for **5b**: yield 0.92 g (39%); ^{1}H NMR (200 MHz) δ 1.50–2.60 (m, 8 H), 1.97 (br s, 3 H), 4.60–4.75 (m, 1 H), 6.70–6.90 (m, 2 H), 6.90–7.05 (br s, 1 H), 7.05–7.30 (m, 3 H), 7.35–7.50 (m, 2 H), 7.85–7.95 (m, 2 H), 8.00–8.15 (m, 2 H), 8.60–9.10 (br s, 2 H); MS m/z 466 (M^+).

Cyclic *O*-Acetyl Derivative 5b (n = 3). A solution of **3b** (1.95 g, 6.89 mmol) in CH_2Cl_2 (80 mL) and a solution of (+)-4 (1.96 g, 6.89 mmol) and Et_3N (1.39 g, 13.78 mmol) in CH_2Cl_2 (80 mL) were synchronously added dropwise to CH_2Cl_2 (700 mL) with a Micro Feeder at room temperature over 24 h. After stirring for further 6 h, the solution was washed twice with water. The organic layer was dried ($MgSO_4$) and then evaporated. The residue was purified by flash chromatography (50% EtOAc in hexane) to give **5b** (1.92 g, 56%): ^{1}H NMR (60 MHz) δ 1.1–1.9 (m, 12 H), 2.00 (s, 3 H), 4.5–4.9 (m, 1 H), 6.8–7.6, 7.8–8.2, and 8.5–8.7 (m, 14 H); MS m/z 494 (M^+).

Cyclic Diamide Alcohol 6a (n = 2). A methanolic solution of KOH (1 N, 2.7 mL) was added to a solution of **5a** (0.63 g, 1.35 mmol) in MeOH (130 mL), and the mixture was stirred at room temperature overnight. Silica gel (3 g) was added to the mixture, and the mixture was evaporated. The product absorbed on the silica gel was chromatographed over silica gel (EtOAc) to give **6a** (0.46 g, 80%) as an amorphous powder:[8] $[\alpha]^{20}_D$ +66.1° (c 1.0, acetone); IR (KBr) 3650–3200, 1680 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.00–3.00 (m, 9 H), 3.25–3.60 (m, 1 H), 6.60–6.80 (m, 1 H), 6.80–6.95 (m, 1 H), 6.95–7.30 (m, 4 H), 7.30–7.60 (m, 2 H), 7.85–8.00 (m, 2 H), 8.00–8.15 (m, 2 H), 8.50–9.00 (br s, 2 H); HRMS m/z (M^+) calcd for $C_{27}H_{24}N_2O_3$ 424.1787, found 424.1779.

Cyclic Diamide Alcohol 6b (n = 3). An aqueous solution of NaOH (6 N, 0.65 mL) was added to a solution of **5b** (1.92 g, 3.89 mmol) in MeOH (30 mL), and the mixture was stirred at room temperature overnight. The product was absorbed on silica gel as for **6a** and chromatographed over silica gel (70% EtOAc in hexane) to give **6b** as an amorphous powder (1.51 g, 86%): $[\alpha[^{20}_D$ +61.7° (c 1.0, acetone); IR (KBr) 3650–3200, 1680 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.10–2.55 (m, 13 H), 3.20–3.28 (m, 1 H), 6.80–7.15 (m, 4 H), 7.15–7.35 (m, 2 H), 7.35–7.55 (m, 2 H), 7.90–8.00 (m, 2 H), 8.00–8.15 (m, 2 H), 8.58 (d, J = 8.0 Hz, 1 H), 8.74 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (50 MHz) δ 18.3, 19.0, 33.6, 35.0, 36.7, 37.2, 65.5, 118.2–135.1 (17 signals for aromatic carbons), 171.8, 173.7; HRMS m/z (M^+) calcd for $C_{29}H_{28}N_2O_3$ 452.2100, found 452.2119.

Five-Membered Lactone 7a. A solution of 1% (v/v) trifluoroacetic acid (TFA) in toluene (5 mL) was added dropwise to a solution of **6a** (10 mg, 0.024 mmol) in toluene (5 mL) at −20 °C. The solution was stirred at −20 °C overnight. The same workup for **7b** gave **7a** as an amorphous powder (9.2 mg, 92%, 71% de by HPLC): $[\alpha]^{20}_D$ +41.4° (c 0.43, $CHCl_3$); IR (KBr) 3600–3200, 1770, 1680 cm^{-1}; ^{1}H NMR (200 MHz, 47% de) δ 1.53–2.48 (m, 8 H), 3.45 (br s, 2 H), 3.90–4.09 (m, 0.753 H), 4.27–4.43 (m, 0.265 H), 6.82–6.92 (m, 1 H), 7.05–7.35 (m, 6 H), 7.35–7.46 (m, 1 H), 7.75–8.05 (m, 4 H), 8.42–8.58 (m, 1 H); ^{13}C NMR (50 MHz) δ 27.7, 28.5, 31.2, 33.3, 79.4, 112.2–141.2 (aromatic carbons), 170.6, 176.7 for the major diastereomer; δ 27.8, 28.6, 30.9, 33.0, 79.6, 112.2–141.2 (aromatic carbons), 170.5, 176.8 for the minor diastereomer; HRMS m/z (M^+) calcd for $C_{27}H_{24}N_2O_3$ 424.1787, found 424.1788.

Six-Membered Lactone 7b. A solution of 4% (v/v) TFA in CH_2Cl_2 (200 mL) was added dropwise to a solution of **6b** (2.0 g, 4.42 mmol) in CH_2Cl_2 (200 mL) at −20 °C over 2.5 h. The mixture was stirred at −20 °C overnight. After adding dropwise a solution of pyridine (9.86 g, 0.125 mol) in CH_2Cl_2 (50 mL), the mixture was washed twice with water. The solution was dried ($MgSO_4$) and evaporated. The residue was chromatographed over silica gel (EtOAc) to give **7b** as an amorphous powder (1.75 g, 88%, 97% de): $[\alpha]^{20}_D$ +20.0° (c 0.55, $CHCl_3$); IR (KBr) 3600–3200, 1722, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 1.30–1.44 (m, 3 H), 1.44–1.60 (m, 2 H), 1.69–1.93 (m, 3 H), 1.98–2.16 (m, 2 H), 2.36–2.45 (m, 1 H), 2.50–2.58 (m, 1 H), 3.92–4.00 (m, 0.015 H), 4.07–4.16 (m, 0.985 H), 4.73–4.84 (br s, 2 H), 6.88–6.93 (m, 1 H), 7.15–7.30 (m, 5 H), 7.40–7.45 (m, 1 H), 7.78–8.03 (m, 4 H), 8.57 (d, J = 10.0 Hz, 1 H); ^{13}C NMR (50 MHz) δ 18.4, 20.7, 27.4, 29.3, 34.4, 36.9, 80.0, 112.4–141.1 (19 signals of aromatic carbon), 171.2, 171.8; HRMS m/z (M^+) calcd for $C_{29}H_{28}N_2O_3$ 452.2099, found 452.2096.

(−)-7-Hydroxy-4-heptanolide (11a). To a solution of **7a** (0.30 g, 0.71 mmol, 47% de) in CH_2Cl_2 (1 mL) were added successively Et_3N (87 mg, 0.86 mmol) and acetic anhydride (87 mg, 0.86 mmol). After being stirred at room temperature overnight, the mixture was evaporated. The residue was dissolved in dry EtOH (20 mL) and heated with LiCl (0.30 g, 7.1 mmol) and $NaBH_4$ (0.27 g, 7.1 mmol) at 70 °C for 4 h. After filtering off inorganic materials, the solution was evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), and the solution was filtered. The filtrate was evaporated to give **10a** (0.30 g, 100%). To a solution of **10a** (0.30 g, 0.64 mmol) in dioxane (1.5 mL) was added 3 N HCl (2 mL). After heating at 70 °C for 30 min, the mixture was diluted with EtOAc (50 mL). The solution was washed with 3 N HCl, dried ($MgSO_4$), and evaporated. Taking the following three steps, the residue was purified to give **11a** as an oil (29 mg, 28%): (1) flash chromatography (EtOAc), (2) silica gel preparative TLC (EtOAc), and (3) ODS reversed-phase chromatography (20% MeOH in water). The lactone alcohol **11a**: $[\alpha]^{25}_D$ −24.2° (c 0.33, EtOH); IR (neat) 3700–3100, 1760 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.60–2.00 (m, 5 H), 2.06 (s, 1 H), 2.27–2.50 (m, 1 H), 2.50–2.65 (m, 2 H), 3.66–3.74 (m, 2 H), 4.50–4.65 (m, 1 H); ^{13}C NMR (50 MHz) δ 27.9, 28.3, 28.8, 31.9, 61.8, 81.1, 177.7; HRMS m/z (M^+ − 1) calcd for $C_7H_{13}O_3$ 145.0865, found 145.0837.

Determination of the ee of 11a. The lactone alcohol (−)-**11a** (26.7 mg, 0.185 mmol) dissolved in CH_2Cl_2 (0.2 mL) was treated with *tert*-butyldimethylsilyl chloride (42 mg, 0.28 mmol) and Et_3N (28 mg, 0.28 mmol) at room temperature overnight. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ twice and with saturated NaCl. The solution was dried ($MgSO_4$) and evaporated to give the protected lactone (45.4 mg, 95%).

Methyllithium (1.6 M in ether, 0.2 mL, 0.32 mmol) was added to this protected lactone (21.0 mg, 0.081 mmol) in dry THF (0.2 mL) at −78 °C. After being stirred at room temperature for 30 min, the mixture was diluted with ether (20 mL) and washed successively with 1% tartaric acid, saturated $NaHCO_3$, and saturated NaCl. The solution was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (50% EtOAc in hexane) to give the diol as an oil (11.8 mg, 50%). The methyl signal (originally δ 1.23) in the ^{1}H NMR of this diol was split into four base-line-separated peaks, indicating 47% ee by a shift reagent: ^{1}H NMR (200 MHz) δ 3.02 and 3.22 (the *S* isomer), 3.13 and 3.61 (the *R* isomer); condition, **12** (10 mg), $Eu(hfc)_3$ (8 mg), $CDCl_3$ (0.6 mL).

Reduction of 7b To Give the Diol 10b. Starting from **7b** (1.74 g, 3.85 mmol, 97% de), the same operation as for **10a** gave **10b** (1.92 g, 100%): ^{1}H NMR (200 MHz) δ 1.00–2.15 (m, 14 H), 1.82 (s, 3 H), 3.25–3.45 (m, 1 H), 3.61 (q, J = 6.0 Hz, 2 H), 6.95–7.07 (m, 2 H), 7.18–7.32 (m, 4 H), 7.40–7.51 (m, 2 H), 7.90–8.10 (m, 4 H), 8.27–8.37 (m, 2 H).

(+)-9-Hydroxy-5-nonanolide (11b). To a solution of the diol **10b** (1.00 g, 2.01 mmol) in CH_2Cl_2 (30 mL), was added *p*-toluenesulfonic acid monohydrate (0.46 g, 2.4 mmol). After being stirred at room temperature for 2 h, the solution was washed successively with 3 N HCl, saturated $NaHCO_3$, and saturated NaCl. After drying ($MgSO_4$), silica gel (5 g) was added to the

solution, and then the mixture was evaporated. The product absorbed on silica gel was chromatographed over silica gel (EtOAc) to give **11b** as an oil (0.15 g, 44%): $[\alpha]^{23}_D$ +49.5° (*c* 1.82, EtOH); ^{1}H NMR (200 MHz) δ 1.35–2.02 (m, 10 H), 2.33–2.70 (m, 2 H), 2.86 (s, 1 H), 3.56–3.68 (m, 2 H), 4.23–4.38 (m, 1 H).

(+)-5-Hexadecanolide (13). A solution of dimethyl sulfoxide (330 mg, 4.2 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of oxalyl chloride (0.25 g, 2.0 mmol) in CH_2Cl_2 (2 mL) between −50 and −60 °C. The mixture was stirred for 10 min, and then **11b** (0.15 g, 0.89 mmol) in CH_2Cl_2 (0.9 mL) was added to the mixture. After this mixture was stirred at the same temperature for 30 min, Et_3N (0.9 g, 8.9 mmol) was added. The mixture was stirred for 10 min and then warmed up to room temperature. The mixture was diluted with water (5 mL) and extracted twice with CH_2Cl_2. The combined extracts were washed successively with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl. The solution was dried ($MgSO_4$) and evaporated. Distillation gave the aldehyde (84 mg, 56%): bp 160–170 °C (0.8 mmHg); ^{1}H NMR (200 MHz) δ 1.40–2.00 (m, 8 H), 2.30–2.70 (m, 4 H), 4.25–4.40 (m, 1 H), 9.79 (t, *J* = 1.2 Hz, 1 H).

A solution of this aldehyde (84 mg, 0.49 mmol) in dry THF (0.6 mL) was added at 0 °C to the ylide solution prepared from heptyltriphenylphosphonium bromide (0.24 g, 0.54 mmol), Bu^{t}OK (58 mg, 0.52 mmol), and dry THF (3.2 mL). After the mixture was stirred at room temperature for 50 min, a solution of TFA (0.042 mL) in THF (0.4 mL) was added to the mixture under ice cooling. After being stirred at room temperature for 10 min, the mixture was diluted with hexane (50 mL) and then washed successively with saturated $NaHCO_3$ and saturated NaCl. The solution was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (33% EtOAc in hexane) to give the alkene (47 mg, 38%).

This alkene (47 mg, 0.19 mmol) was hydrogenated over 5% palladium carbon (50 mg) in ether (10 mL) under ambient pressure at room temperature for 2 h. The mixture was filtered, and the filtrate was evaporated to give **13** (46 mg, 97%): $[\alpha]^{20}_D$ +39.17° (*c* 1.08, THF) [lit.[12] $[\alpha]^{20}_D$(max) +39.97° (*c* 1, THF)]. An optically pure sample was obtained by recrystallization from hexane: $[\alpha]^{20}_D$ +39.81° (*c* 1.05, THF); mp 40 °C (lit. mp 40–41 °C); IR (KBr) 1720 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.89 (t, *J* = 4.0 Hz, 3 H), 1.15–2.00 (m, 24 H), 2.33–2.70 (m, 2 H), 4.20–4.36 (m, 1 H). Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.31; H, 11.94.

Di-*tert*-butyl 4-(Hydroxymethyl)heptanedioate (16). A solution of di-*tert*-butyl 4-oxoheptanedioate (14.5 g, 50.6 mmol) derived from **1a** in dry THF (73 mL) was added to the ylide solution prepared from methyltriphenylphosphonium bromide (28.9 g, 8.10 mmol), Bu^{t}OK (8.52 g, 76.0 mmol), and dry THF (435 mL). After being stirred at room temperature for 1 h, the mixture was evaporated and filtered. The residue was washed with ether (200 mL). The filtrate and the washing were combined and evaporated. The residue was purified by flash chromatography (15% EtOAc in hexane) to give di-*tert*-butyl 4-methyleneheptanedioate (12.4 g, 86%).

To a solution of this alkene (11.79 g, 41.45 mmol) in dry THF (12 mL) was added a THF solution of 9-borabicyclo[3.3.1]nonane (9-BBN, 0.5 M, 104 mL, 52 mmol) at room temperature. After the mixture was stirred for 1 h, water (2.4 mL) and 3 N NaOH (13.8 mL) were added successively. Then, 30% H_2O_2 (13.8 mL) was added dropwise while maintaining the temperature below 50 °C. After being stirred at room temperature for 1 h, the mixture was diluted with ether (300 mL). The organic layer was separated and washed with saturated NaCl. The solution was dried (K_2CO_3) and evaporated. The residue was purified by flash chromatography (36% EtOAc in hexane) to give **16** as an oil (11.0 g, 88%): ^{1}H NMR (200 MHz) δ 1.44 (s, 18 H), 1.47–1.77 (m, 5 H), 2.28 (t, *J* = 8.0 Hz, 4 H), 2.51 (br s, 1 H), 3.44–3.55 (m, 2 H).

4-(Acetoxymethyl)heptanedioyl Dichloride (17). The reaction procedures were the same as those for **3b**. The yields of the intermediary products are as follows: di-*tert*-butyl 4-(acetoxymethyl)heptanedioate, 97%; 4-(acetoxymethyl)heptanedioic acid, 100%. The dichloride **17** (99%): ^{1}H NMR (200 MHz) δ 1.68–1.84 (m, 5 H), 2.08 (s, 3 H), 2.96–3.08 (m, 4 H), 4.03 (d, *J* = 4.0 Hz, 2 H).

Cyclic Diamide Alcohol 19. Starting from the dichloride **17** (6.40 g, 23.78 mmol), the same operation for **5b** gave the cyclic *O*-acetyl derivative **18** (4.83 g, 42%). To a solution of **18** (4.83 g, 10.1 mmol) in EtOH (150 mL) was added a solution of KOH (1.13 g, 20.1 mmol) in MeOH (10 mL). The mixture was stirred at room temperature for 3 h. The mixture was evaporated, and the residue was chromatographed over silica gel (EtOAc) to give **19** (3.86 g, 88%) as an amorphous powder:[8] $[\alpha]^{20}_D$ +75.7° (*c* 1.0, acetone); IR (KBr) 3650–3200, 1680 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.10–3.70 (m, 12 H), 6.60–7.70, 7.90–8.20, and 8.70–9.10 (m, 14 H); HRMS *m/z* (M^+) calcd for $C_{28}H_{26}N_2O_3$ 438.1943, found 438.1925.

Six-Membered Lactone 20. A solution of 0.2% (v/v) TFA in CH_2Cl_2 (700 mL) was added dropwise to a solution of **19** (2.79 g, 6.36 mmol) in CH_2Cl_2 (700 mL) at 40 °C. The mixture was stirred at 40 °C for 4.5 h. The same workup for **7b** gave **20** as an amorphous powder (2.18 g, 78%, >99% de): $[\alpha]^{20}_D$ +44.3° (*c* 0.4, $CHCl_3$); IR (KBr) 3650–3250, 1726, 1680 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.23–1.43 (m, 3 H), 1.56–1.68 (m, 1 H), 1.71–1.81 (m, 1 H), 2.07 (t, *J* = 7.3 Hz, 2 H), 2.27–2.38 (m, 1 H), 2.43–2.53 (m, 1 H), 3.6 (br s, 2 H), 3.63–3.70 (m, 1 H), 3.95–4.02 (m, 1 H), 6.87–6.93 (m, 1 H), 7.12–7.32 (m, 5 H), 7.39–7.47 (m, 1 H), 7.78–8.04 (m, 4 H), 8.48–8.57 (m, 1 H), 7.05 (br s, 1 H); ^{13}C NMR (50 MHz) δ 24.8, 26.8, 28.6, 31.5, 34.2, 72.7, 115.3–138.6 (24 signals for aromatic carbons), 170.8, 171.4; HRMS *m/z* (M^+) calcd for $C_{28}H_{26}N_2O_3$ 438.1943, found 438.1911.

(+)-4-(3-Hydroxypropyl)-5-pentanolide (23). The same operation for **11b** gave **(+)-23** as an oil in an overall yield of 16% from **20**. **(+)-23**: $[\alpha]^{25}_D$ +5.2° (*c* 1.82, EtOH); IR (neat) 3700–3100, 1726 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.30–1.80 (m, 5 H), 1.80–2.13 (m, 2 H), 2.40–2.73 (m, 2 H), 3.67 (t, *J* = 6.2 Hz, 2 H), 3.90–4.05 (m, 1 H), 4.30–4.42 (m, 1 H); ^{13}C NMR (50 MHz) δ 25.3, 27.7, 28.9, 29.6, 32.5, 62.2, 73.6, 172.0; HRMS *m/z* ($M^+ - H_2O$) calcd for $C_8H_{12}O_2$ 140.0837, found 140.0838.

(−)-2-(2-Cyanoethyl)-4-pentenoic Acid (24). To a solution of Bu^{t}OK (0.14 g, 1.25 mmol) in Bu^{t}OH (3 mL) was added a solution of diethyl allylmalonate (5.0 g, 25 mmol) in Bu^{t}OH (2 mL). A solution of acrylonitrile (1.59 g, 30 mmol) in Bu^{t}OH (2 mL) was added dropwise to the mixture at room temperature. After the mixture was stirred for 1 h, 2 N HCl (0.6 mL) was added and then the mixture was evaporated. The residue was dissolved in a mixture of ether (100 mL) and water (50 mL). The organic layer was separated and washed successively with saturated $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), distillation gave diethyl allyl(2-cyanoethyl)malonate (6.11 g, 97%): bp 155 °C (0.9 mmHg).

To a solution of this malonate derivative (17.2 g, 67.8 mmol) in EtOH (35 mL) was added a solution of KOH (15.2 g, 0.27 mol) in water (75 mL). After stirring at room temperature for 2 days, the mixture was neutralized with 6 N HCl (42 mL). After the EtOH was distilled off under reduced pressure, the residue was dissolved in a mixture of EtOAc (300 mL) and 1 N HCl (100 mL). The organic layer was separated and evaporated to give allyl(2-cyanoethyl)malonic acid (13.4 g, 100%).

This diacid (7.0 g, 35.6 mmol) was set in a distillation flask and heated at 150 °C (bath temperature) under reduced pressued (1–2 mmHg). The distillate was collected and dissolved in ether (50 mL). The solution was extracted with saturated $NaHCO_3$ (30 mL × 3). The combined aqueous solution was made acidic with concentrated HCl and extracted with EtOAc (60 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated to give **(±)-24** (3.8 g, 70%).

The **(±)**-acid **24** (10.3 g, 67.2 mmol) and (−)-α-methylbenzylamine (8.45 g, 67.2 mmol) were dissolved in EtOH (100 mL). After evaporation, the residue was dissolved in CH_2Cl_2 (50 mL). The solution was diluted with ether (400 mL) and allowed to stand at room temperature for 1 day, during which time crystallization took place. The salt was collected (7.15 g) and recrystallized twice from the same solvents. The salt thus obtained (4.05 g) was dissolved in 3 N HCl (50 mL), and the solution was extracted with EtOAc (50 mL × 3). After drying ($MgSO_4$), evaporation gave **(−)-24** as an oil (2.24 g): $[\alpha]^{15}_D$ −13.8° (*c* 4.73, EtOH); IR (neat) 3700–2300, 2250, 1710, 1645, 995, 925 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.78–2.12 (m, 2 H), 2.24–2.73 (m, 5 H), 5.05–5.21 (m, 2 H), 5.64–5.88 (m, 1 H), 11.15 (br s, 1 H); HRMS *m/z* (M^+) calcd for $C_8H_{11}NO_2$ 153.0790, found 153.0804.

(*S*)-(−)-2-Allyl-5-pentanolide (26). To a solution of **(−)-24** ($[\alpha]^{15}_D$ −13.8°, 0.77 g, 5.0 mmol) in dry toluene (5 mL) was added DIBAL-H (1.5 M in toluene, 10 mL, 15 mmol) at −70 °C. After

the mixture was stirred for 1 h, water (1 mL) was added at -70 °C. The mixture was poured into a mixture of 6 N HCl (5 mL) and EtOAc (20 mL). The aqueous layer was separated and extracted with EtOAc (30 mL × 2). The combined organic solution was washed with saturated NaCl, dried ($MgSO_4$), and then evaporated. The residue (0.49 g) was dissolved in EtOH (10 mL), and $NaBH_4$ (0.35 g, 9.3 mmol) was added to the solution. After being stirred at room temperature for 1.5 h, the mixture was poured into a mixture of 2 N HCl (20 mL) and EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (30 mL × 2). The combined organic solution was dried ($MgSO_4$) and evaporated. The residue was heated in benzene (15 mL) containing *p*-toluenesulfonic acid (40 mg) with a Dean-Stark apparatus for 30 min. The benzene solution was washed successively with saturated $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), evaporation gave (-)-**26** (0.17 g, 24%): $[\alpha]^{18}_D$ -27.8° (*c* 3.05, MeOH); ^1H NMR (200 MHz) δ 1.48-1.68 (m, 1 H), 1.82-1.96 (m, 2 H), 1.96-2.18 (m, 1 H), 2.20-2.40 (m, 1 H), 2.49-2.70 (m, 2 H), 4.25-4.39 (m, 2 H), 5.03-5.19 (m, 2 H), 5.73-5.94 (m, 1 H); HRMS *m/z* (M^+) calcd for $C_8H_{12}O_2$ 140.0837, found 140.0867.

4-(Hydroxymethyl)-6-heptenenitrile (27). To a solution of (-)-**24** ($[\alpha]^{15}_D$ -13.8°, 1.45 g, 9.5 mmol) in ether (5 mL) was added an ethereal solution of diazomethane. After evaporation, the residue was dissolved in dry EtOH (130 mL) and heated with LiCl (1.6 g, 3.8 mmol) and $NaBH_4$ (1.45 g, 3.8 mmol) at 50 °C for 10 h. After filtering off inorganic materials, the solution was evaporated. The residue was dissolved in CH_2Cl_2 (100 mL), and the solution was washed successively with 2 N HCl, saturated $NaHCO_3$, and saturated NaCl. After drying ($MgSO_4$), evaporation gave **27** as an oil (1.14 g, 86%): ^1H NMR (200 MHz) δ 1.60-1.87 (m, 3 H), 2.06-2.18 (m, 2 H), 2.45 (t, *J* = 7.0 Hz, 2 H), 3.46-3.73 (m, 2 H), 5.00-5.20 (m, 2 H), 5.64-5.80 (m, 1 H).

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-hydroxyheptanenitrile (28). To a mixture of **27** (1.13 g, 8.11 mmol) and imidazole (0.66 g, 9.7 mmol) in dry CH_2Cl_2 (13 mL) was added *tert*-butyldimethylsilyl chloride (1.5 g, 9.7 mmol) under ice cooling. After being stirred at room temperature for 24 h, the mixture was washed successively with water and saturated NaCl. The solution was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (18% EtOAc in hexane) to give the silyl ether (1.56 g, 76%).

To a solution of this silyl ether (1.56 g, 6.14 mmol) in dry THF (6 mL) was added a THF solution of 9-BBN (0.5 M, 14.7 mL, 7.4 mmol) at room temperature. After the mixture was stirred for 1.5 h, water (0.3 mL) and 30% H_2O_2 (2.1 mL) were added successively below 50 °C. Then 3 N NaOH (2.1 mL) was added to the mixture. After being stirred at room temperature for 1 h, the mixture was diluted with ether (100 mL). The organic layer was separated and washed with saturated NaCl. The solution was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (36% EtOAc in hexane) to give **28** as an oil (1.24 g, 75%): ^1H NMR (200 MHz) δ 0.04 (s, 6 H), 0.80 (s, 9 H), 1.12-1.80 (m, 8 H), 2.34 (t, *J* = 7.2 Hz, 2 H), 3.36-3.66 (m, 4 H).

7-(Benzyloxy)-4-(hydroxymethyl)heptanenitrile (29). A solution of **28** (1.22 g, 4.5 mmol) in dry THF (5 mL) was added dropwise to a solution of Bu^tOK (0.61 g, 5.4 mmol) in dry THF (3.5 mL). After the mixture was stirred at room temperature for 5 min, benzyl bromide (0.93 g, 5.4 mmol) was added. The mixture was stirred at room temperature for 10 h and then diluted with water (20 mL). The mixture was extracted with ether (30 mL × 3), and the combined extracts were washed with saturated NaCl and dried ($MgSO_4$). After evaporation, the residue was purified by flash chromatography (18% EtOAc in hexane) to give the benzyl ether as an oil (1.18 g, 72%).

This benzyl ether (1.15 g, 3.18 mmol) was dissolved in dioxane (25 mL) and treated with 6 N H_2SO_4 (2.5 mL) at room temperature overnight. The mixture was diluted with water (50 mL) and extracted withe ether (50 mL × 3). The combined extracts were washed successively with saturated $NaHCO_3$ and saturated NaCl and then dried ($MgSO_4$). Evaporation gave **29** as an oil (0.69 g, 87%): ^1H NMR (200 MHz) δ 1.32-1.48 (m, 2 H), 1.54-1.88 (m, 5 H), 2.41 (t, *J* = 7.0 Hz, 2 H), 3.48 (t, *J* = 6.2 Hz, 2 H), 3.52-3.70 (m, 2 H), 4.50 (s, 2 H), 7.33 (s, 5 H).

(-)-4-(3-Hydroxypropyl)-5-pentanolide [(-)-23]. To a solution of **29** (0.67 g, 2.7 mmol) in EtOH (10 mL) was added a solution of KOH (4.5 g, 81 mmol) in water (5 mL). The mixture was heated at 50 °C for 8 h and then diluted with water (30 mL). After being washed with ether, the aqueous solution was made acidic with 6 N HCl and extracted with EtOAc (50 mL × 3). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was heated in benzene (30 mL) containing *p*-toluenesulfonic acid (70 mg) with a Dean-Stark apparatus for 30 min. The benzene solution was washed successively with saturated $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), the solution was evaporated. The residue was purified by flash chromatography (56% EtOAc in hexane) to give the protected lactone (0.53 g, 80%): $[\alpha]^{20}_D$ -2.7° (*c* 5.2, EtOH).

This protected lactone (0.20 g, 0.81 mmol) was dissolved in EtOAc (4 mL) and hydrogenated over 26% $Pd(OH)_2/C$ (0.2 g) under ambient pressure at room temperature for 2 h. The mixture was filtered, and the filtrate was evaporated to give (-)-**23** (0.122 g, 95%) as an oil: $[\alpha]^{20}_D$ -3.1° (*c* 5.05, EtOH).

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Supplementary Material Available: Experimental details for synthesis and lactonization of the cyclic amide alcohol **6c** and the linear amide alcohols **14a,b** and **15a,b** as well as detailed results of the MM2 calculation including the parameters used herein plus ^1H and/or ^{13}C NMR spectra for most all compounds (52 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Amarolide, a Quassinoid Bitter Principle

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The first total synthesis of amarolide (1), a bitter tasting quassinoid having a picrasane skeleton with 10 chiral centers, is described in racemic form. The synthesis of (±)-1 was accomplished stereoselectively in 35 steps and 0.5% overall yield from a known tricyclic compound **7**. An orthoester Claisen rearrangement and a lead tetraacetate oxidation were utilized as key reactions to prepare hydroxy ketone **14** with a complete picrasane skeleton. This hydroxy ketone was transformed into 1 in 18 steps that included 1,3-carbonyl transposition, introduction of hydroxyl groups at C-2 and C-11 positions, and oxidation of an ether to afford a δ-lactone.

Quassinoid is a generic name for terpenoids represented by amarolide (1), quassin (2), and so on, that have been isolated from plants of Simaroubaceae family.[1] Most of these quassinoids have a bitter taste, and some of them

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