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# Asymmetric Halolactonization Reactions. 3.[1] Asymmetric Synthesis of optically Active Anthracyclinones[2]

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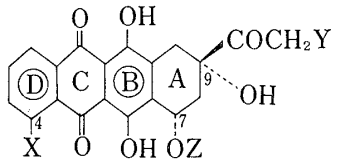
The asymmetric bromolactonization of (*S*)-N-(α,β-unsaturated)acylproline ((*S*)-**17a**) prepared from the α,β-unsaturated acid (**10a**) was found to occur stereoselectively to give the bromolactone (**18a**) in which one diastereomer (**18Aa**) was predominant. Debromination of **18a** followed by acidic hydrolysis, afforded the (*R*)-α-hydroxy acid ((*R*)-**12a**) in 92% optical purity. Reaction of (*R*)-**12a** with methyllithium gave the (*R*)-α-hydroxy ketone ((*R*)-**9a**), a model compound of the optically active anthracyclinone AB ring system, in good yield.

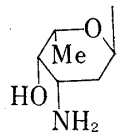
When the reaction scheme established by the model study was applied to **10b, c**, which possess the AB and ABCD ring systems of anthracyclinones (**2**), (*R*)-α-hydroxy acid methyl esters ((*R*)-**21b, c**) could be prepared in 97% and 87% optical yields, respectively. Alkaline hydrolysis of optically pure (*R*)-**21b, c** independently prepared from the pure debrominated lactones (**19Ab, c**) gave (*R*)-**12b, c**. Although the reaction of tetracyclic (*R*)-**12c** with methyllithium did not proceed in the expected manner, bicyclic (*R*)-**12b** was successfully converted to optically pure (*R*)-**9b**, which has previously been utilized as a starting material for the synthesis of optically active natural and unnatural **2**.

**Keywords**——asymmetric synthesis; halolactonization reaction; anthracyclines; anthracyclinones; debromination; hydrolysis; optically active α-hydroxy acids; optically active α-hydroxy ketones; (*S*)-N-(α,β-unsaturated)acylprolines; α,β-unsaturated acids

The anthracycline antibiotics, adriamycin (**1a**),[4,5] daunorubicin (**1b**),[4,5] and carmino mycin (**1c**),[6] are of current interest because of their promising antineoplastic activity against various experimental tumors and certain types of human cancer.[4,7] Though chemotherapy employing **1a, b** is hampered by a number of undesirable side effects, including dose-related cardiotoxicity,[4,8] studies on the structure-activity relationship have shown that unnatural 4-demethoxy analogs of **1a, b**, 4-demethoxyadriamycin (**1d**) and 4-demethoxydaunorubicin (**1e**), show improved therapeutic properties.[4,9]




| | X | Y | | X | Y |
|---|---|---|---|---|---|
| a : | OMe | OH | d : | H | OH |
| b : | OMe | H | e : | H | H |
| c : | OH | H | | | |




1 : Z=

2 : Z=H

1) Part 2: S.-s. Jew, S. Terashima, and K. Koga, *Tetrahedron*, in press.
2) Parts of the present results have appeared in the two preliminary communications. S. Terashima, S.-s. Jew, and K. Koga, *Tetrahedron Lett.*, **1977**, 4507, and **1978**, 4937.
3) Location: *Hongo, Bunkyo-ku, Tokyo 113, Japan*; *a*) To whom all correspondence should be addressed.
4) F. Arcamone, *Lloydia*, **40**, 45 (1977).
5) *a*) F. Arcamone, G. Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.*, **1969**, 1007; *b*) D.W. Henry, "Cancer Chemotherapy," ACS Sympodium Series, 30, published by the American Chemical Society, Washington D.C., 1976, p. 15.
6) *a*) G.R. Pettit, J.J. Einck, C.L. Herald, R.H. Ode, R.B. Von Dreele, P. Brown, M.G. Brazhnikova, and G.F. Gause, *J. Am. Chem. Soc.*, **97**, 7387 (1975); *b*) M.C. Wani, H.L. Taylor, M.E. Wall, A.T. McPhail, and K.D. Onan, *ibid.*, **97**, 5955 (1975).
7) *Chem. Eng. News*, April 12, p. 18, (1976).
8) *a*) G. Rosen, N. Wollner, C. Tan, S.J. Wu, S.I. Hajdu, W. Cham, G.J. D'Angio, and M.L. Murphy, *Cancer*, 33, 384 (1974); *b*) J.F. Halazun, H.R. Wagner, J.F. Gaeta, and L.F. Sinks, *ibid.*, 33, 545 (1974).
9) F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. Di Marco, A.M. Casazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, **60**, 829 (1976).

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Due to the clinical utility of anthracyclines (**1**),[4,5b] various syntheses of the anthracyclinones (**2**), the aglycones of **1**, have been reported, yielding racemic modifications.[10–13] Efficient procedures for transforming daunomycinone (**2b**) into adriamycinone (**2a**)[12] and for coupling a suitably protected sugar with **2**[12,14] have been developed. Although regiospecific synthesis of **2b**[11a,13,15a,16] and exploitation of an effective synthetic scheme yielding 4-demethoxydaunomycinone (**2e**)[4,9,10a,15b,17–21] are currently attracting considerable interest, it is still difficult to obtain optically active **2**[22] and no reports have appeared in the area of asymmetric synthesis.

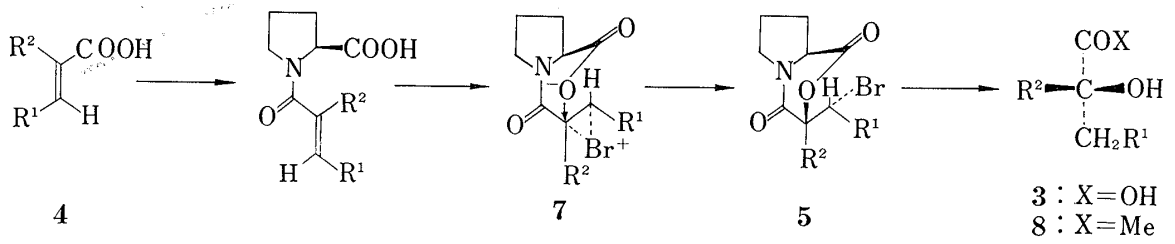


Chart 1

As shown in Chart 1, we have developed a very efficient asymmetric synthesis which provides optically active α,α-disubstituted-α-hydroxy acids (**3**) from α,β-unsaturated acids (**4**) *via* the bromolactones (**5**) in more than 89% optical yields.[24] Detailed mechanistic studies described in the preceding paper,[1] have shown that the asymmetric bromolactonization reaction of (*S*)-N-(α,β-unsaturated)acylprolines (**6**), which constitutes the key step of the synthetic route, proceeds highly stereoselectively and regiospecifically *via* the bromonium ions (**7**), resulting in the predominant formation of **5**.

Since conversion of **3** to optically active α-hydroxy ketones (**8**) corresponding to partial structures of **2** (C-9 position), seems to be readily achievable, application of this asymmetric synthesis to the preparation of optically active **2** should be fruitful.

This report describes a model study undertaken to investigate the feasibility of this route, and our subsequent successful asymmetric synthesis of optically active **2**, based on the results obtained from the model study.

10) *a*) C.M. Wong, D. Popien, R. Schwenk, and J. TeRaa, *Can. J. Chem.*, **49**, 2712 (1971); *b*) C.M. Wong, R. Schwenk, D. Popien, and T-L. Ho, *ibid.*, **51**, 466 (1973).
11) *a*) A.S. Kende, J. Belletire, T.J. Bentley, E. Hume, and J. Airey, *J. Am. Chem. Soc.*, **97**, 4425 (1975); *b*) A.S. Kende, Y-g. Tsay, and J.E. Milles, *ibid.*, **98**, 1967 (1976).
12) T.H. Smith, A.N. Fujiwara, W.W. Lee, H.Y. Wu, and D.W. Henry, *J. Org. Chem.*, **42**, 3653 (1977).
13) F. Suzuki, S. Trenbeath, R.D. Gleim, and C.J. Sih, *J. Org. Chem.*, **43**, 4159 (1978), and preceding papers.
14) E.M. Acton, A.N. Fujiwara, and D.W. Henry, *J. Med. Chem.*, **17**, 659 (1974).
15) *a*) T.R. Kelly, J.W. Gillard, R.N. Goerner, Jr., and J.M. Lyding, *J. Am. Chem. Soc.*, **99**, 5513 (1977); *b*) T.R. Kelly and W-G. Tsang, *Tetrahedron Lett.*, **1978**, 4457.
16) J.S. Swenton and P.W. Raynolds, *J. Am. Chem. Soc.*, **100**, 6188 (1978), and preceding papers.
17) F.A.J. Keredesky and M.P. Cava, *J. Am. Chem. Soc.*, **100**, 3635 (1978).
18) J. Alexander and L.A. Mischer, *Tetrahedron Lett.*, **1978**, 3403.
19) R.B. Garland, J.R. Palmer, J.A. Schulz, P.B. Sollmann, and R. Pappo, *Tetrahedron Lett.*, **1978**, 3669.
20) J.R. Wiseman and N.I. French, *Tetrahedron Lett.*, **1978**, 3765.
21) K. Krohn and K. Tolkiehn, *Tetrahedron Lett.*, **1978**, 4023.
22) Optically active **2b** and **2e** have been prepared by chemical resolution of the racemic intermediate,[4,9,23] and the synthesis of optically active **1a** utilizes optically active 7-deoxydaunomycinone, obtained by reductive cleavage of natural **1b**, as a relay compound.[12]
23) F. Arcamone, L. Bernardi, B. Patelli, and A. Di Marco, Ger. Offen., 2601785 (1976).
24) S.-s. Jew, S. Terashima, and K. Koga, *Tetrahedron*, in press.

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## Results and Discussion

### I. Asymmetric Synthesis of (*R*)(—)-2-Acetyl-1,2,3,4-tetrahydro-2-naphthol ((*R*)-9a): A Model Compound of the Optically Active Anthracyclinone AB Ring System

In order to evaluate the applicability of the previously reported asymmetric reaction to the preparation of optically active **2**, the synthesis of (*R*)-2-acetyl-1,2,3,4-tetrahydro-2-naphthol((*R*)-**9a**), a model compound of the optically active anthracyclinone AB ring system, was first attempted.

Among two possible substrates for the asymmetric synthesis, 3,4-dihydro-2-naphthoic acid (**10a**) and 1,4-dihydro-2-naphthoic acid (**11**), the former acid (**10a**)[25] was selected as the starting material. The established reaction mechanism for the asymmetric bromolactonization[1,24] clearly suggests that **10a** and **11** can be converted to the desired (*R*)- and undesired (*S*)-α-hydroxy acids ((*R*)- and (*S*)-**12a**) *via* the bromonium ions (**13** and **14**, respectively), as visualized in Chart 2.

The reaction scheme employed for the preparation of (*R*)-**9a** is shown in Chart 3.

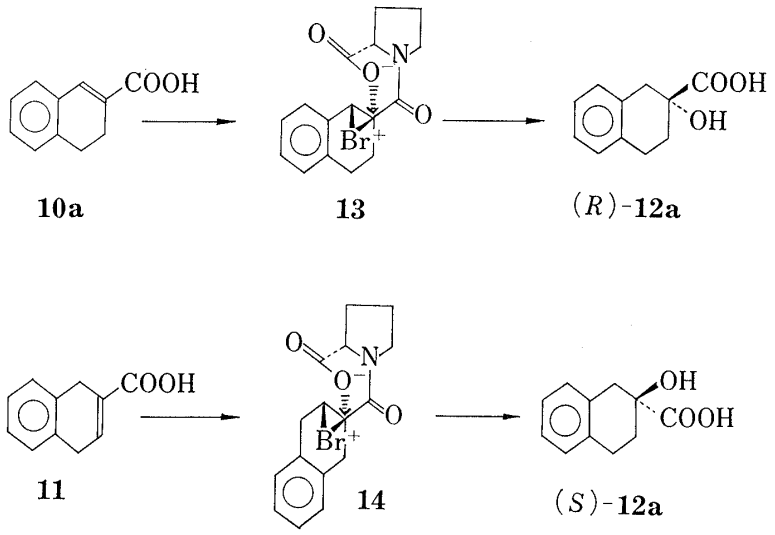


Chart 2

Condensation of (*S*)-ethyl prolinate ((*S*)-**15**),[26] $[\alpha]_D^{20}$ —42.6° (ethanol), with **10a**[25] in the presence of diethyl phosphorocyanidate (DEPC)[27] and triethylamine (TEA) in N,N-dimethylformamide (DMF), afforded (*S*)-ethyl N-acylprolinate ((*S*)-**16a**), $[\alpha]_D^{20}$ —18.6° (ethanol), in 91% yield. Subsequent alkaline hydrolysis of (*S*)-**16a** almost quantitatively yielded (*S*)-N-acylproline ((*S*)-**17a**), $[\alpha]_D^{20}$ —93.3° (chloroform).

The asymmetric bromolactonization of the potassium salt of (*S*)-**17a**, which was obtained by treating (*S*)-**17a** with potassium t-butoxide in DMF,[28] was effected by using N-bromosuccinimide (NBS) in DMF to afford the crude bromolactone (**18a**) (**18Aa**: **18Ba** 96:4) (*vide infra*), $[\alpha]_D^{20}$ —68.6° (chloroform), in 79% yield as the sole reaction product. Recrystallization of crude **18a** readily gave pure **18Aa**, $[\alpha]_D^{20}$ —88.8° (chloroform). The absolute configurations

25) *a*) H.L. Holmes and L.W. Trevoy, "Organic Syntheses," Coll. Vol. III, p. 302; *b*) E.B. Hershbergs and L.F. Fieser, *ibid.*, Coll. Vol. II, p. 196; *c*) W.E. Truce and C.E. Ols, *J. Am. Chem. Soc.*, **74**, 4721 (1952).
26) M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 279 (1975).
27) T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, *Tetrahedron*, **32**, 2211 (1976).
28) In the same way as with (*S*)-N-(*trans*-α-methylcinnamoyl)proline (see ref. 24), direct bromolactonization of (*S*)-**17a** was found to be very sluggish.

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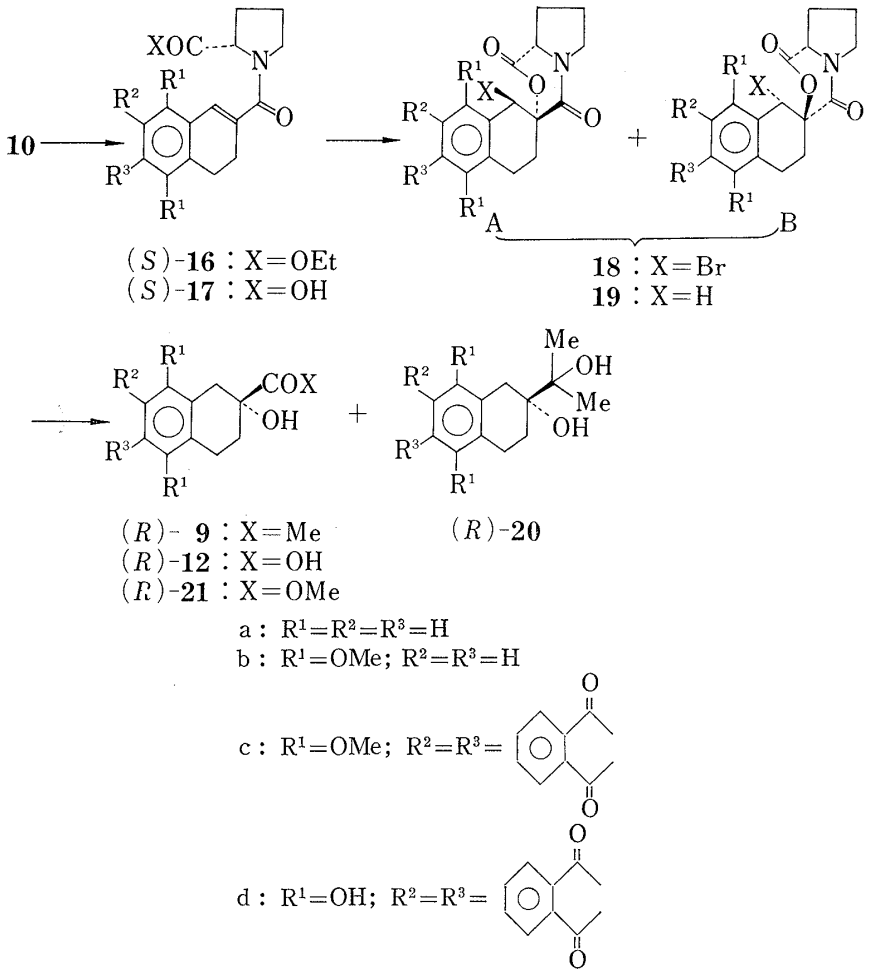


Chart 3

of **18Aa** and **18Ba** and that of **12a**, derivable from the predominantly formed diastereomer (**18Aa**) (*vide infra*), were tentatively assigned according to the previous mechanistic studies, which had established that the asymmetric bromolactonization proceeded preferentially *via* the bromonium ion (**13**).[1,24]

Debromination of crude **18a** with tri-*n*-butyltin hydride[29] in bromobenzene using a catalytic amount of azobisisobutyronitrile (AIBN) afforded the crude lactone (**19a**), $[\alpha]_D^{20}$ −156° (chloroform), in 76% yield. Crude **19a** was subjected to acidic hydrolysis, giving a 93% yield of (*R*)-**12a**, $[\alpha]_D^{20}$ −15.0° (acetone). The spectral and chromatographic properties of (*R*)-**12a** was identical with those of the racemic acid ((±)-**12a**) prepared from 2-tetralone[30] according to the reported method.[31]

On the other hand, when pure **18Aa** was successively debrominated and hydrolyzed in a similar manner, optically pure (*R*)-**12a**, $[\alpha]_D^{20}$ −16.3° (acetone), could be obtained *via* pure **19Aa**, $[\alpha]_D^{20}$ −154° (chloroform). Comparison of the two sets of the optical rotations for (*R*)-**12a** clearly showed that the optical purity of (*R*)-**12a** directly derived from crude **18a** and the formation ratio of **18Aa** to **18Ba** were 92% and 96 : 4, respectively.

Treatment of (*R*)-**12a**, $[\alpha]_D^{20}$ −15.0° (acetone), 92% optically pure, with an excess of methyllithium in ether,[32] followed by careful quenching with aqueous hydrochloric acid

29) H.G. Kuivila, *Symthesis*, **1970**, 499.
30) J.H. Burckhalter and J.R. Campbell, *J. Org. Chem.*, **26**, 4232 (1961).
31) A.M. El-Abbady and S.H. Doss, *J. Chem. U.A.R.*, **8**, 33 (1965).
32) M.J. Jorgenson, "Preparation of Ketones from the Reaction of Organolithium Reagents with Carboxylic Acid" in "Organic Reactions," ed. by W.G. Dauben, Vol. 18, John-Wiley and Sons, New York, 1970, p. 1.

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and purification on a silica gel column, gave (*R*)-**9a**, $[\alpha]_D^{20}$ −33.1° (chloroform), and (*R*)-tertiary alcohol ((*R*)-**20a**),[33] $[\alpha]_D^{20}$ −33.3° (chloroform), in 67% and 20% yields, respectively. The optically active α-hydroxy ketone ((*R*)-**9a**), obtained as an oil, showed spectral and chromatographic properties identical with those of the racemic ketone ((±)-**9a**) similarly prepared from (±)-**12a**. The structure of (*R*)-**20a**, isolated as the sole by-product, was confirmed by its spectral data.

The successful synthesis of (*R*)-**9a** from **10a** clearly shows that the asymmetric synthesis of optically active **2** is possible using the reaction scheme exploited in the preceding papers.[1,24] Studies along this line were carried out as described in the next section.

## II. Asymmetric Synthesis of Optically Active Anthracyclinones

Based on the results obtained above, the asymmetric synthesis of optically active **2** was attempted using two different types of α,β-unsaturated acids (**10b**, **c**) with the AB and ABCD ring systems of **2**, as reaction substrates.

Compounds **10b**, **c** were selected as reaction substrates because (*R*)-**9b**, **c**, expected to be produced by the asymmetric synthesis, are well-known key intermediates for the synthesis of optically active **2**.[4,9,10,23]

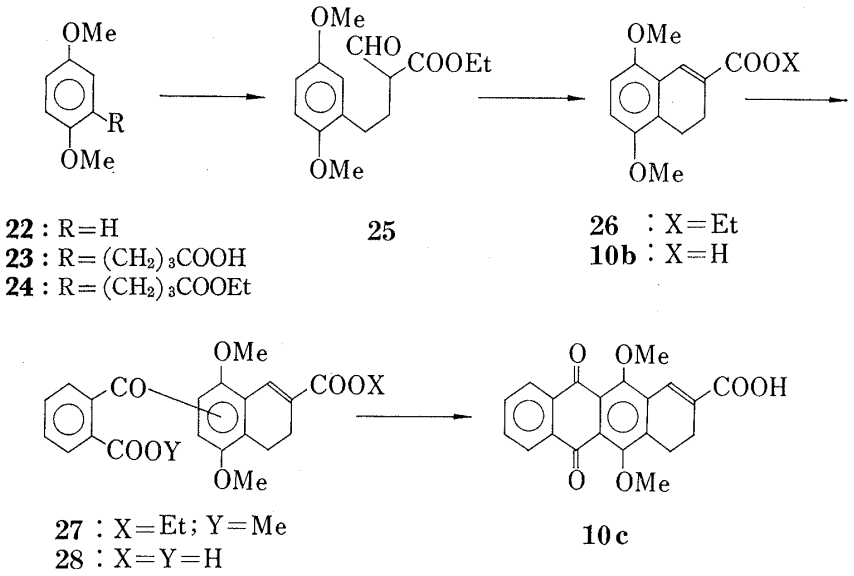


Chart 4

Preparation of **10b**, **c** was carried out following the reaction scheme shown in Chart 4. Thus, acylation of 1,4-dimethoxybenzene (**22**) with succinic anhydride[34] followed by Clemmensen reduction[35] according to the reported procedure,[34,35] afforded the known acid (**23**), which on esterification gave the corresponding ethyl ester (**24**) in 63% yield. Condensation of **24** with ethyl formate by the use of sodium hydride gave the α-formyl ester (**25**) in 48% yield with 54% recovery of the starting material. Cyclization of **25** was effected by treatment with a mixture of 90% phosphoric acid and 98% sulfuric acid, giving the ethyl ester (**26**) in 43% yield. The ester (**26**) was hydrolyzed under alkaline conditions to afford **10b** in 97% yield. On the other hand, acylation of **26** with *o*-methoxycarbonylbenzoyl

33) This compound was erroneously described as (*S*)(−)-2(2-hydroxy-2-methyl)propyl-1,2,3,4-tetrahydro-2-naphthol, mp 72—76°, in the preliminary communication.[2]

34) J.A. Moore and M. Rahm, *J. Org. Chem.* **26**, 1109 (1961).

35) *a*) L.F. Fieser, M.D. Gates, Jr., and G.W. Kilmer, *J. Am. Chem. Soc.*, **62**, 2966 (1940); *b*) E.L. Martin, *ibid.*, **58**, 1438 (1936).

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chloride[36] in the presence of aluminum chloride afforded a regioisomeric mixture of the diesters (**27**)[37] in 48% yield with 56% recovery of starting **26**. Alkaline hydrolysis of **27** followed by treatment with liquid hydrogen fluoride, furnished **10c** in 58% yield from **27**.

Since the preparation of **10b, c** was thus completed, the asymmetric synthesis of (*R*)-**9b, c** was examined as shown in Chart 3.

Condensation of **10b** with (*S*)-**15** as described for **10a** quantitatively afforded (*S*)-**16b**, $[\alpha]_D^{20}$ −10.3° (ethanol), which was then saponified to (*S*)-**17b**, $[\alpha]_D^{20}$ −3.0° (2 N NaOH), in 97% yield. The same successive treatments of **10c** as those of **10a, b** gave (*S*)-**17c**, $[\alpha]_D^{20}$ −30.4° (benzene), *via* (*S*)-**16c**, $[\alpha]_D^{20}$ −13.4° (chloroform).

The asymmetric bromolactonization of the potassium salt of (*S*)-**17b** with NBS proceeded in a highly stereoselective manner, as was the case for (*S*)-**17a**, giving crude unstable **18b** (**18Ab**: **18Bb** 98.5: 1.5)(*vide infra*), $[\alpha]_D^{20}$ +36.0° (chloroform), in 87% yield. Immediate debromination[29] of crude **18b** yielded crude **19b** as a mixture of the two diastereomers (**19Ab** and **19Bb**), $[\alpha]_D^{20}$ −138° (chloroform), in 95% yield. The predominantly formed **19Ab** could be isolated in a pure state, $[\alpha]_D^{20}$ −152° (chloroform), on recrystallization of crude **19b**. The structures of **18Ab, Bb** and **19Ab, Bb** were assigned on the basis of reported mechanistic studies[1,24] and the fact that the predominantly formed **18Ab** could be transformed to optically pure (*R*)-**9b**[9,23] *via* **19Ab** (*vide infra*). Similar asymmetric bromolactonization of (*S*)-**17c** followed by debromination of the crude extremely unstable **18c**(**18Ac**: **18Bc** 93.5: 6.5)(*vide infra*), gave crude **19c** as a mixture of the two diastereomers (**19Ac** and **19Bc**) in 50% overall yield from (*S*)-**17c**. Recrystallization of crude **19c** afforded the predominantly produced **19Ac** in a pure state, $[\alpha]_D^{20}$ +11.9° (chloroform). Assignment of the structures of **18Ac, Bc** and **19Ac, Bc** was carried out by assuming that the asymmetric bromolactonization of tetracyclic (*S*)-**17c** proceeded through the same reaction mechanism as that of bicyclic (*S*)-**17a, b**.

Recrystallized **19Ab** was subjected to acid hydrolysis, and the reaction product, obtained as a mixture of (*R*)-**12b** and the methyl ester ((*R*)-**21b**), was directly treated with diazomethane to afford optically pure (*R*)-**21b**, $[\alpha]_D^{20}$ −34.5° (chloroform), in 87% overall yield. Since the same treatments of crude **19b** gave partially optically active (*R*)-**21b**, $[\alpha]_D^{20}$ −33.3° (chloroform), the optical purity of (*R*)-**21b** obtained from crude **19b** and the formation ratio of **18Ab** to **18Bb** could be calculated as 97% and 98.5: 1.5, respectively. In contrasts, partial hydrolytic cleavage of the two methyl ether groups occurred when crude **19c** was treated under the same conditions as **19b**.[38] Therefore, crude **19c** was hydrolyzed under more severe conditions, and the resulting trihydroxy acid ((*R*)-**12d**) was successively esterified with diazomethane and methylated with dimethyl sulfate,[17] to give partially optically active (*R*)-**21c**, $[\alpha]_D^{20}$ −6.8° (acetone), in 87% yield from **19c**. Purification of this sample by preparative tlc and recrystallization gave optically pure (*R*)-**21c**, $[\alpha]_D^{20}$ −7.8° (acetone). The optical purity of (*R*)-**21c** obtained from crude **19c** and the formation ratio of **18Ac** to **18Bc** could be calculated as 87% and 93.5: 6.5, respectively, assuming the purified (*R*)-**21c** to be optically pure.

Alkaline hydrolysis of optically pure (*R*)-**21b, c** readily afforded optically pure (*R*)-**12b, c**, $[\alpha]_D^{20}$ −39.3° (chloroform) and $[\alpha]_D^{20}$ +13.6° (chloroform), in 96% and 100% yields, respectively.

Unfortunately, the reaction of (*R*)-**12c** with methyllithium (10—30 equivalents) in a mixture of ether and tetrahydrofuran[32] was found to afford many products, all of which were more polar than the authentic α-hydroxy ketone[39] on tlc analysis. This might be due to the preferential attack of methyllithium on the anthraquinone carbonyl moiety. However,

36) *a*) G. Losse and H. Raue, *Chem. Ber.*, **98**, 1522 (1965); *b*) B. Taub, H.A. Leipold, and J.B. Hino, *J. Org. Chem.*, **24**, 2062 (1959).
37) Separation of the two regioisomers was not attempted.
38) Facile cleavage of the methyl ether groups may be due to the presence of the anthraquinone nucleus.
39) Authentic samples of racemic and optically active α-hydroxy ketone ((±)- and (*R*)-**9c**) were kindly provided by Prof. C.M. Wong and Prof. F. Arcamone, respectively.

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treatment of the other α-hydroxy acid ((*R*)-**12b**) with methylithium in ether successfully gave optically pure (*R*)-**9b**, $[\alpha]_D^{20}$ −48.2° (chloroform), in 63% yield, with concomitant formation of the undesired (*R*)-**20b**.[40] The melting point and optical rotation of (*R*)-**9b** thus obtained were identical with those reported for a sample prepared by chemical resolution.[9,23] Since the synthetic route to (*R*)-**9c** from (*R*)-**9b** was completely established by Arcamone *et al.*,[9,23] it has become possible to prepare optically pure (*R*)-**9c** *via* (*R*)-**9b** by asymmetric synthesis.

Optically pure tetracyclic (*R*)-**9c** has been elaborated to optically pure **2e**,[9,23] the aglycone of **1e** which has improved therapeutic properties,[4,9] and the reported synthesis of optically active **2b**[23] utilized optically pure bicyclic (*R*)-**9b** as a key intermediate. Moreover, a reaction scheme for converting optically active **2b** to optically active **2a** has been developed by Smith *et al.*[12] Accordingly, our successful synthesis of optically pure (*R*)-**9b** constitutes the first asymmetric synthesis of several structural types of optically active **2**.

## Experimental[41]

**(*S*)(—)-Ethyl N-(3,4-Dihydro-2-naphthoyl)prolinate ((*S*)-16a)**——A DMF solution (60 ml) of DEPC[27] (7.17 g, 44.0 mmol) and a DMF solution (60 ml) of TEA (4.05 g, 40.0 mmol) were successively added over 5 min to a stirred solution of **10a**[25] (mp 117—119°) (7.12 g, 40.0 mmol) and (*S*)-**15**[26] ($[\alpha]_D^{20}$ −42.6° (*c*=2.01, ethanol)) (6.41 g, 44.8 mmol) in DMF (60 ml) at 0° under a nitrogen atmosphere. The mixture was stirred at 0° for 2 hr, then at room temperature for 48 hr under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (1.8 l), and the ethyl acetate solution was washed successively with 5% HCl, $H_2O$, satd. NaCl, and satd. $NaHCO_3$. Filtration and concentration *in vacuo* afforded crude (*S*)-**16a** as a yellow oil (13.9 g, quantitative yield), which was subjected to column chromatography (silica gel, solvent ether) to give almost pure (*S*)-**16a** as colorless needles (11.1 g, 91%), mp 55—57°. Recrystallization from hexane–ether gave pure (*S*)-**16a** as colorless needles (9.5 g, 79%), mp 56—57°, $[\alpha]_D^{20}$ −18.6° (*c*=1.03, ethanol). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1750 (ester), 1650 (olefin), 1610 (amide). NMR (in $CDCl_3$): 1.27 (3H, t, *J*=7 Hz, $C\underline{H}_3CH_2$), 1.64—2.40 (4H, m, $C\underline{H}_2C\underline{H}_2CH_2N$), 2.40—3.20 (4H, m, $C\underline{H}_2C\underline{H}_2C$=), 3.72 (2H, t, *J*=6 Hz, $C\underline{H}_2N$), 4.16 (2H, q, *J*=7 Hz, $CH_3C\underline{H}_2$), 4.58 (1H, t, *J*=6 Hz, NC<u>H</u>CO), 6.77 (1H, s, C<u>H</u>=), 7.12 (4H, s, $C_6\underline{H}_4$). *Anal.* Calcd. for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.22; H, 7.02; N, 4.73.

**(*S*)(—)-N-(3,4-Dihydro-2-naphthoyl)proline ((*S*)-17a)**——An aqueous solution (50 ml) of KOH (85% pure) (2.56 g, 0.039 mol) was added to an ethanolic solution (50 ml) of (*S*)-**16a** ($[\alpha]_D^{20}$ −18.6° (*c*=1.03, ethanol)) (9.09 g, 0.030 mol). After stirring for 5 hr at room temperature, the mixture was concentrated to one-fourth of the original volume, and washed with ether. The alkaline aqueous solution was acidified (pH≒2) with conc. HCl, and a compound that separated was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with satd. NaCl. Filtration and concentration *in vacuo* gave pure (*S*)-**17a** as a colorless oil (3.1 g, 98%), $[\alpha]_D^{20}$ −93.3° (*c*=2.16, chloroform). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1730 (acid), 1630 (olefin), 1570 (amide). NMR (in $CDCl_3$): 1.73—2.43 (4H, m, $C\underline{H}_2C\underline{H}_2CH_2N$), 2.43—3.15 (4H, m, $C\underline{H}_2C\underline{H}_2C$=), 3.69 (2H, t, *J*=6 Hz, $C\underline{H}_2N$), 4.60 (1H, t, *J*=7 Hz, NC<u>H</u>CO), 6.75 (1H, s, C<u>H</u>=), 7.09 (4H, s, $C_6\underline{H}_4$), 8.65 (1H, s, COO<u>H</u>). This sample was immediately used for the next bromolactonization reaction.

**1(*R*)-Bromo-1′,4′-dioxo-3,4,6′,7′,8′,8′a(*S*)-hexahydro-spiro[naphthalene-2(*S*) (1H), 3′(*S*)(4′H)-1H-pyrrolo-[2,1-*c*][1,4]oxazine] (18Aa) and Its 1(*S*),2(*R*),3′(*R*)-Isomer (18Ba) (Bromolactonization Reaction of (*S*)-17a[28])**——A DMF solution (45 ml) of potassium *t*-butoxide (1.89 g, 16.9 mmol) and a DMF solution (15 ml) of NBS (6.00 g, 33.7 mmol) were successively added to a stirred solution of (*S*)-**17a** [$[\alpha]_D^{20}$ −93.3° (*c*=2.16, chloroform)) (4.57 g, 16.9 mmol) in DMF (15 ml) at −20° under a nitrogen atmosphere. After stirring at −20° for 2 hr, then at room temperature for 20 hr,[42] the reaction mixture was diluted with ethyl acetate (800 ml),

40) This compound was erroneously named (*R*)-5,8-dimethoxy-2(2-hydroxy-2-methyl)propyl-1,2,3,4-tetrahydro-2-naphthol in the preliminary communication.[2]

41) All melting and boiling points are uncorrected. IR spectra measurements were performed with a JASCO DS-402G infrared spectrometer and a JASCO IRA-1 grating infrared spectrometer. NMR spectra were measured with a Hitachi R-24 high resolution spectrometer (60 MHz) and a JEOL JNM-PS-100 spectrometer (100 MHz). All signals are expressed as the ppm downfield from tetramethylsilane used as an internal standard (δ value). The following abbreviations are used: singlet(s), doublet (d), triplet(t), quartet(q), multiplet(m), broad (br). Measurements of optical rotations were carried out using a Yanaco OR-50 automatic polarimeter. Mass spectra were taken with a JMS SG-2 mass spectrometer. All reactions were performed using anhyd. solvents, and the combined organic extracts obtained in each experiment were dried over anhyd. $Na_2SO_4$ or anhyd. $MgSO_4$ before filtration and concentration *in vacuo*.

42) The reaction time was erroneously given as 48 hr in the preliminary communication.[2]

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and the organic solution was washed successively with 5% $NaHCO_3$, $H_2O$, and satd. NaCl. Filtration and concentration *in vacuo* gave crude **18a** (a mixture of **18Aa** and **18Ba**) as yellow needles (4.64 g, 79%), mp 166—170°, $[\alpha]_D^{20}$ −68.6° ($c$=1.01, chloroform). IR and NMR spectra of this sample were identical with those of pure **18Aa** prepared from this sample. Since this sample gave (*R*)-**12a** which was 92% optically pure, the formation ratio of **18Aa** to **18Ba** can be calculated as 96: 4.

Recrystallization of a part of the crude **18a** (3.03 g) from hexane–ether afforded the predominantly formed **18Aa** in a pure state (1.4 g, 46% recovery), colorless needles, mp 196—197°, $[\alpha]_D^{20}$ −88.8° ($c$=1.02, chloroform). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1760 (lactone), 1683 (amide). NMR (in $CDCl_3$): 1.60—2.70 (4H, m, $C\underline{H}_2C\underline{H}_2CH_2N$), 2.70—3.40 (4H, m, $C\underline{H}_2C\underline{H}_2CHBr$), 3.3—3.8 (2H, m, $C\underline{H}_2N$), 4.30—4.80 (1H, m, $NC\underline{H}CO$), 5.31 (1H, d, $J$=3 Hz, $C\underline{H}Br$),[43] 6.97—7.27 (4H, s, $C_6\underline{H}_4$). *Anal.* Calcd. for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.61; N, 4.00. Found: C, 54.62; H, 4.61; N, 3.89.

**1′,4′-Dioxo-3,4,6′,7′,8′,8′a(*S*)-hexahydro-spiro[naphthalene-2(*R*)(1H),3′(*R*)(4′H)-1H-pyrrolo[2,1-*c*][1,4]-oxazine] (19Aa) and Its 2(*R*),3′(*R*)-Isomer (19Ba)**——A bromobenzene solution (18.5 ml) of tri-*n*-butyltin hydride[29] (13.3 g, 45.7 mmol) was added to a solution of crude **18a** (mp 166—177°, $[\alpha]_D^{20}$ −68.6° ($c$=1.01, chloroform)) (4.00 g, 11.4 mmol) in bromobenzene (74 ml). The mixture was stirred at *ca.* 65° for 9 hr under an argon atmosphere with adding a bromobenzene solution (5 ml) of AIBN (31.3 mg, 0.191 mmol) every 3 hr. The bromobenzene was removed from the reaction mixture *in vacuo* (10 mmHg, bath temperature <60°), and the residue was purified by column chromatography (silica gel, using first hexane, then hexane–ether 2: 1). The organotin compounds were eluted from the column by hexane, then elution with hexane–ether (2: 1) afforded fractions containing **19a**. The latter fractions were combined and concentrated *in vacuo* to give crude **19a** (a mixture of **19Aa** and **19Ba**) as pale yellow needles (2.34 g, 76%), mp 165—173°, $[\alpha]_D^{20}$ −156° ($c$=0.502, chloroform). This sample showed the same spectral (IR and NMR) properties as pure **19Aa** prepared as described below.

Debromination of pure **18Aa** (mp 196—197°, $[\alpha]_D^{20}$ −88.8° ($c$=1.02, chloroform) (1.10 g, 3.14 mmol) as described for crude **18a**, gave crude **19Aa** as colorless needles (667 mg, 79%), mp 166—173°, $[\alpha]_D^{20}$ −151° ($c$=0.531, chloroform), after the removal of bromobenzene *in vacuo* and purification by column chromatography. Recrystallization from chloroform–ether afforded an analytical sample of **19Aa** as colorless needles, mp 173—175°, $[\alpha]_D^{20}$ −154° ($c$=0.500, chloroform). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1758 (lactone), 1662 (amide). NMR (in $CDCl_3$): 1.88—2.55 (6H, m, $C\underline{H}_2C\underline{H}_2CH_2N$ and $CH_2C\underline{H}_2CCH_2$), 2.55—3.05 (2H, m, $C\underline{H}_2CH_2CCH_2$), 3.20 (2H, br s, $CH_2CH_2CC\underline{H}_2$), 3.40—3.90 (2H, m, $C\underline{H}_2N$), 4.35 (1H, br t, $J$=9.6 Hz, $NC\underline{H}CO$), 7.05 (4H, m, $C_6\underline{H}_4$). *Anal.* Calcd. for $C_{16}H_{17}NO_3$-1/5$H_2O$: C, 69.96; H, 6.38; N, 5.09. Found: C, 69.96; H, 6.19; N, 5.21.

**(*R*)(—)-2-Hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid ((*R*)-12a)**——A mixture of crude **19a** (mp 165—173°, $[\alpha]_D^{20}$ −156° ($c$=0.502, chloroform)) (1.50 g, 5.53 mmol) and 36% HCl (50 ml) was heated under reflux for 3 hr. After being saturated with NaCl, the acidic solution was extracted with ethyl acetate, and the combined ethyl acetate layers were re-extracted with satd. $NaHCO_3$. The bicarbonate solutions were combined, acidified (pH≒2) with conc. HCl, and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with satd. NaCl. Filtration and concentration *in vacuo* gave partially optically active (*R*)-**12a** as colorless needles (0.99 g, 93%), mp 71—76°, $[\alpha]_D^{20}$ −15.0° ($c$=2.06, acetone). The spectral (IR and NMR) properties of this sample were identical with those of optically pure (*R*)-**12a** prepared as described below. Since optically pure (*R*)-**12a** shows $[\alpha]_D^{20}$ −16.3° ($c$=2.07, acetone), the optical purity of this sample and the formation ratio of **18Aa** to **18Ba** can be calculated as 92% and 96: 4, respectively.

When similar acidic hydrolysis was carried out using pure **19Aa** (mp 173—175°, $[\alpha]_D^{20}$ −154° ($c$=0.500, chloroform)) (388 mg, 1.43 mmol), optically pure (*R*)-**12a**, mp 88—94°, $[\alpha]_D^{20}$ −15.3° ($c$=2.08, acetone), was obtained as colorless needles (260 mg, 94%) after concentration of the combined ethyl acetate extracts. Recrystallization of this sample from hexane-ether gave an analytical sample of optically pure (*R*)-**12a** as colorless needles, mp 94—96°, $[\alpha]_D^{20}$ −16.3° ($c$=2.07, acetone). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1718 (acid). NMR (in $CDCl_3$–DMSO-$d_6$): 1.80—2.10 (2H, m, $CH_2C\underline{H}_2CCH_2$), 2.10—3.30 (2H, m, $C\underline{H}_2CH_2CCH_2$), 2.80 (1H, d, $J$=16 Hz, one of $CH_2CH_2CC\underline{H}_2$), 3.30 (1H, d, $J$=16 Hz, one of $CH_2CH_2CC\underline{H}_2$), 6.55 (2H, br s, O$\underline{H}$ and COO$\underline{H}$), 7.04 (4H, s, $C_6\underline{H}_4$). These spectral properties were identical with those of the racemic acid ((±)-**12a**), mp 134—135° (lit.,[31] mp 142—143°), prepared from 2-tetralone[30] according to the reported method.[31]

**(*R*)(—)-2-Acetyl-1,2,3,4-tetrahydro-2-naphthol ((*R*)-9a) and (*R*)(—)-2(1-Hydroxy-1-methyl)ethyl-1,2,3,4-tetrahydro-2-naphthol ((*R*)-20a)**[33]——An ethereal solution of methyllithium[32] (0.93 M solution, 26 ml, 23.6 mmol) was added over 80 min to a stirred solution of (*R*)-**12a** (mp 72—76°, $[\alpha]_D^{20}$ −15.0° ($c$=1.98, acetone), 92% opitically pure) (454 mg, 2.36 mmol) in ether (9 ml) at room temperature under an argon atmosphere. When the addition was complete, the mixture was further stirred at room temperature for 20 min, then injected over 15 min to dil. HCl (36% HCl–$H_2O$ 3: 40) (200 ml) saturated with NaCl. The acidic mixture was extracted with ethyl acetate, and the combined organic extracts were successively washed with 10% $Na_2S_2O_3$ and satd. NaCl. Filtration and concentration *in vacuo* gave a yellow oil (453 mg) which was subjected to column chromatography (silica gel, solvent ether–hexane 2: 1) to give (*R*)-**9a**, 92% optically pure, as a colorless oil (298 mg, 67%), $[\alpha]_D^{20}$ −33.1° ($c$=3.22, chloroform), and (*R*)-**20a** as colorless needles (96 mg, 20%), mp 63—65°, $[\alpha]_D^{20}$ −33.3° ($c$=1.25, chloroform).

43) This signal was found to couple with one of the C-3 protons in a decoupling experiment.

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The following spectral properties were found for (*R*)-**9a**. IR $\nu_{max}^{film}$ $cm^{-1}$: 3450 (OH), 1700 (ketone). NMR (in $CDCl_3$): 1.70—2.10 (2H, m, $CH_2C\underline{H}_2CCH_2$), 2.22 (3H, s, $COC\underline{H}_3$), 2.40—3.10 (2H, m, $C\underline{H}_2CH_2CCH_2$), 2.75 (1H, d, $J$=16 Hz, one of $CH_2CH_2CC\underline{H}_2$), 3.15 (1H, d, $J$=16 Hz, one of $CH_2CH_2CC\underline{H}_2$), 4.40 (1H, br s, O$\underline{H}$), 7.00 (4H, s, $C_6\underline{H}_4$). MS *m/e*: 190 [$M^+$], 172 [$M^+-H_2O$], 147 [$M^+-COCH_3$]. These spectra were identical with those of the racemic ketone ((±)-**9a**), a colorless oil (68% yield), prepared from (±)-**12a** by the same procedure. The oily racemic ketone ((±)-**9a**) gave the corresponding crystalline semicarbazone, mp 221—223°. *Anal.* Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.06; H, 6.95; N, 16.88.

The (*R*)(−)-alcohol ((*R*)-**20a**) formed as a by-product, exhibited the following spectral properties. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3420 (OH). NMR (in $CDCl_3$): 1.23 (6H, s, two $C\underline{H}_3$), 1.50—2.15 (2H, m, $CH_2C\underline{H}_2CCH_2$), 2.55 (2H, s, two O$\underline{H}$), 2.35—3.15 (4H, m, $C\underline{H}_2CH_2CC\underline{H}_2$), 7.01 (4H, s, $C_6\underline{H}_4$). MS *m/e*: 206 [$M^+$], 191 [$M^+-CH_3$]. Formation of the corresponding racemic alcohol ((±)-**20a**), a colorless oil (25% yield), was also observed when the preparation of (±)-**9a** from (±)-**12a** was attempted. The spectral (NMR) properties of (±)-**20a** were identical with those of (*R*)-**20a** cited above.

**Ethyl 4-(2,5-Dimethoxyphenyl)butyrate (24)**——A solution of **23**[34,35] (mp 60—62°) (lit.,[35a] mp 64.5—67°; lit.,[35b] mp 61—62°) (52.4 g, 0.234 mol) and conc. $H_2SO_4$ (few drops; catalytic amount) in ethanol (180 ml) was refluxed for 5 hr. After cooling, satd. $NaHCO_3$ was added to the ethanolic solution, and the mixture was concentrated *in vacuo*. The residue was diluted with ether, and the ethereal mixture was successively washed with satd. $NaHCO_3$, $H_2O$, and satd. NaCl. Filtration and concentration *in vacuo* gave a dark red oil (55 g) which was twice purified by fractional distillation to afford pure **24** as a pale yellow oil (37 g, 63%), bp 155—158° (3 mmHg). IR $\nu_{max}^{film}$ $cm^{-1}$: 1720 (ester). NMR (in $CDCl_3$): 1.19 (3H, t, $J$=7.5 Hz, $C\underline{H}_3CH_2$), 1.56—2.06 (2H, m, $C\underline{H}_2CH_2COOEt$), 2.06—2.46 (2H, m, $C\underline{H}_2COOEt$), 2.46—2.76 (2H, br t, $J$=6.6 Hz, $C\underline{H}_2CH_2CH_2COOEt$), 3.67 (6H, s, two $OC\underline{H}_3$), 4.15 (2H, q, $J$=7.5 Hz, $CH_3C\underline{H}_2$), 6.15 (3H, s, $C_6\underline{H}_3$).

**Ethyl 5,8-Dimethoxy-3,4-dihydro-2-naphthoate (26)**——a) Ethyl 2-Formyl-4-(2,5-dimethoxyphenyl)-butyrate (**25**): An ethereal solution (50 ml) of ethyl formate (42.8 g, 0.578 mol) was added to a stirred mixture prepared by suspending sodium hydride (55% oil dispersion) (12.6 g, 0.289 mol), previously washed with hexane under a nitrogen atmosphere, in ether (68 ml). Next, an ethereal solution (36 ml) of **24** (37.0 g, 0.147 mol) was added over 30 min with stirring. The mixture was stirred at 40—50° for 5 hr. After standing at room temperature overnight, the reaction mixture which had become semisolid, was added to ice-water (300 ml), and the aqueous solution was extracted with ether. The aqueous phase was acidified (pH≒2) with conc. HCl, saturated with NaCl, and extracted with ether. The combined ethereal extracts were filtered and concentrated *in vacuo* to afford crude **25** as a reddish yellow oil (19.8 g, 48%). IR $\nu_{max}^{film}$ $cm^{-1}$: 1730, 1710 (ester), 1680 (CHO). This was used directly for the next step.

The first ethereal extracts were combined, and washed with satd. NaCl. Filtration and concentration *in vacuo* yielded the starting material (**24**) as a pale yellow oil (20.0 g, 54%).

b) Ethyl 5,8-Dimethoxy-3,4-dihydro-2-naphthoate (**26**): The crude ester (**25**) (19.0 g, 70.0 mmol) was added to a mixture of 90% phosphoric acid (84 ml) and 98% sulfuric acid (17 ml) at −10°. The reaction mixture was stirred at 0—10° for 2 hr, then poured into ice-water (380 ml). The acidic aqueous solution was neutralized with 40% NaOH (250 ml) under ice-cooling, and the pale yellow oil that separated was extracted with ether. The combined ethereal extracts were washed with $H_2O$ and satd. $NaHCO_3$. Filtration and concentration *in vacuo* gave crude **26** as a pale yellow oil (16.4 g). This was purified by column chromatography (silica gel, solvent hexane–ether 4: 3) to give pure **26** as pale yellow needles (7.6 g, 43%), mp 74—76°. Recrystallization from hexane–ether gave an analytical sample of **26** as colorless needles, mp 76—77°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1680 (ester). NMR (in $CDCl_3$): 1.34 (3H, t, $J$=7.5 Hz, $C\underline{H}_3CH_2$), 2.30—3.10 (4H, m, $C\underline{H}_2C\underline{H}_2C$=), 3.77 (3H, s, $OC\underline{H}_3$), 3.80 (3H, s, $OC\underline{H}_3$), 4.27 (2H, q, $J$=7.5 Hz, $CH_3C\underline{H}_2$), 6.60 (1H, d, $J$=7.2 Hz, one of the aromatic protons), 6.77 (1H, d, $J$=7.2 Hz, one of the aromatic protons), 7.87 (1H, br s, C$\underline{H}$=). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.72; H, 6.96.

**5,8-Dimethoxy-3,4-dihydro-2-naphthoic Acid (10b)**——A mixture of **26** (7.50 g, 28.6 mmol) and 2 N NaOH (25 ml) in ethanol (50 ml) was heated under reflux for 5 hr. The aqueous solution was concentrated *in vacuo* to one-fourth of the original volume, and the residual solution was diluted with $H_2O$ (50 ml). After washing with ether, the aqueous phase was acidified (pH≒2) with conc. HCl. A white precipitate (**10b**) was collected by filtration and dried *in vacuo*. This weighed 6.50 g (97%) and showed mp>220°. Recrystallization of this sample from ethanol gave an analytical sample of **10b** as colorless needles, mp>220°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1660 (acid). NMR (in $CDCl_3$–DMSO-$d_6$): 2.20—3.00 (4H, $C\underline{H}_2C\underline{H}_2C$=), 3.80 (3H, s, $OC\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 6.75 (1H, d, $J$=10.7 Hz, one of the aromatic protons), 6.93 (1H, d, $J$=10.7 Hz, one of the aromatic protons), 7.82 (1H, br s, C$\underline{H}$=). *Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.95; H, 6.06.

**5,12-Dimethoxy-6,11-dioxo-3,4,6,11-tetrahydronaphthacene-2-carboxylic Acid (10c)**——a) Ethyl 5,8-Dimethoxy-7-(2-methoxycarbonyl)benzoyl-3,4-dihydro-2-naphthoate and Ethyl 5,8-Dimethoxy-6-(2-methoxycarbonyl)benzoyl-3,4-dihydro-2-naphthoate (**27**): Powdered $AlCl_3$ (3.00 g, 22.0 mmol) was added over 1 hr to a mixture of **26** (1.05 g, 4.00 mmol) and *o*-methoxycarbonylbenzoyl chloride[36] (3.97 g, 20.0 mmol) in methylene chloride (10 ml). After stirring at room temperature for 3 hr, the reaction mixture was poured into ice-water (50 ml), and extracted with ethyl acetate. The combined ethyl acetate extracts were washed successively with $H_2O$, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration *in vacuo* gave a mixture

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of the reaction product (**27**) and phthalic anhydride as a red oil (3.1 g). This was dissolved in methanol (2 ml) and the methanolic solution was refluxed for 2 hr to convert the phthalic anhydride to its half methyl ester. The methanolic solution was evaporated down *in vacuo* and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed successively with satd. $NaHCO_3$ and satd. NaCl. Filtration and concentration *in vacuo* gave a brown oil (1.6 g). This was subjected to column chromatography (silica gel, solvent hexane–ether 8: 7) to afford the crude starting material (**26**) as an oil (584 mg, 56% recovery) and a mixture of the regioisomeric diesters (**27**)[37] as a pale yellow oil (820 mg, 48%). IR $\nu_{max}^{film}$ $cm^{-1}$: 1725, 1710, 1700 (ester), 1660 (ketone). NMR (in $CDCl_3$): 1.32 (3H, t, $J$=7 Hz, $C\underline{H}_3CH_2$), 2.32—3.12 (4H, m, $C\underline{H}_2C\underline{H}_2C$=), 3.34 (*ca.* 2.25H, s, $CO_2C\underline{H}_3$), 4.00 (*ca.* 0.75H, s, $CO_2C\underline{H}_3$), 3.50 (*ca.* 0.75H, s, $OC\underline{H}_3$), 3.70 (*ca.* 2.25H, s, $OC\underline{H}_3$), 3.65 (*ca.* 0.75H, s, $OC\underline{H}_3$), 3.81 (*ca.* 2.25H, s, $OC\underline{H}_3$), 4.17 (2H, q, $J$=7 Hz, $CH_3C\underline{H}_2$), 7.22—8.12 (6H, m, aromatic protons). This sample was used immediately for the next step.

b) 5,8-Dimethoxy-7-(2-carboxy)benzoyl-3,4-dihydro-2-naphthoic Acid and 5,8-Dimethoxy-6-(2-carboxy)benzoyl-3,4-dihydro-2-naphthoic Acid (**28**): A mixture of crude **27** (6.80 g, 16.0 mmol) and 2 N NaOH (33 ml, 66 mmol) in ethanol (66 ml) was heated under reflux for 3 hr. After concentration *in vacuo*, the residue was diluted with satd. NaCl (50 ml) and washed with ethyl acetate. The aqueous phase was acidified with conc. HCl and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with satd. NaCl. Filtration and concentration *in vacuo* gave a crude mixture of the two regioisomeric acids (**28**)[37] as a pale yellow powder (5.3 g, 87%). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1670 (acid), 1640 (ketone). NMR (in $CDCl_3$–DMSO-$d_6$): 2.25—3.15 (4H, m, $C\underline{H}_2C\underline{H}_2C$=), 3.35 (*ca.* 2.25H, br s, $OC\underline{H}_3$), 3.49 (*ca.* 0.75H, br s, $OC\underline{H}_3$), 3.80 (*ca.* 2.25H, br s, $OC\underline{H}_3$), 4.03 (*ca.* 0.75H, br s, $OC\underline{H}_3$), 7.05—8.85 (6H, m, aromatic protons and C$\underline{H}$=), 9.92 (2H, br s, two COO$\underline{H}$). This sample was used directly for the next cyclization.

c) 5,12-Dimethoxy-6,11-dioxo-3,4,6,11-tetrahydronaphthacene-2-carboxylic Acid (**10c**): A solution of crude **28** (5.10 g, 13.4 mmol) in liquid hydrogen fluoride (160 ml) was stirred at room temperature for 43 hr. Concentration of the reaction mixture *in vacuo* gave a reddish brown semisolid (4.7 g) which was triturated with ethyl acetate. Filtration and drying *in vacuo* gave crude **10c** as a brown powder (3.28 g, 67%). A part of the brown powder was recrystallized from acetic acid to afford an analytical sample of **10c** as pale yellow needles, mp>250°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1686 (acid), 1665 (quinone). NMR (in $CDCl_3$–DMSO-$d_6$): 2.98—3.78 (4H, $C\underline{H}_2C\underline{H}_2C$=), 3.71 (3H, s, $OC\underline{H}_3$), 3.75 (3H, s, $OC\underline{H}_3$), 7.58—8.08 (5H, m, aromatic protons and C$\underline{H}$=). *Anal.* Calcd. for $C_{21}H_{16}O_6$–1/3$H_2O$: C, 68.10; H, 4.53. Found: C, 67.78; H, 4.28.

**(*S*)(—)-Ethyl N-(5,8-Dimethoxy-3,4-dihydro-2-naphthoyl)prolinate** ((*S*)-**16b**)——Treatments of **10b** (6.24 g, 26.2 mmol) in the same way as **10a** gave crude (*S*)-**16b** as a pale yellow oil (10.3 g, quantitative yield) after concentration of the combined ethyl acetate extracts *in vacuo*. Purification of crude (*S*)-**16b** by column chromatography (silica gel, solvent ether) afforded pure (*S*)-**16b** as a colorless oil (8.3 g, 83%), $[\alpha]_D^{20}$ −10.3° ($c$=2.28, ethanol). IR $\nu_{max}^{film}$ $cm^{-1}$: 1730 (ester), 1635 (olefin), 1603 (amide). NMR (in $CDCl_3$): 1.27 (3H, t, $J$=7.5 Hz, $C\underline{H}_3CH_2$), 1.70—3.10 (8H, m, $C\underline{H}_2C\underline{H}_2C$= and $C\underline{H}_2C\underline{H}_2CH_2N$), 3.50—3.92 (2H, m, $C\underline{H}_2N$), 3.78 (6H, s, two $OC\underline{H}_3$), 4.17 (2H, q, $J$=7.5 Hz, $CH_3C\underline{H}_2$), 4.50 (1H, m, NC$\underline{H}$CO), 6.15 (1H, d, $J$=10.7 Hz, one of the aromatic protons), 6.29 (1H, d, $J$=10.7 Hz, one of the aromatic protons), 7.21 (1H, br s, C$\underline{H}$=).

**(*S*)(—)-Ethyl N-(5,12-Dimethoxy-6,11-dioxo-3,4,6,11-tetrahydronaphthacene-2-carbonyl)prolinate** ((*S*)-**16c**)——Treatments of **10c** (3.00 g, 8.24 mmol) in the same way as **10a** afforded a dark red oil (4.51 g) after concentration of the combined ethyl acetate extracts *in vacuo*. Purification by column chromatography (silica gel, solvent ether–ethyl acetate 3: 1) gave pure (*S*)-**16c** as a red oil (1.94 g, 48%), $[\alpha]_D^{20}$ −14.4° ($c$=0.560, chloroform). Trituration with ethanol, followed by recrystallization from the same solvent, afforded an analytical sample of (*S*)-**16c** as a yellow powder, mp 68—70°, $[\alpha]_D^{20}$ −13.4° ($c$=0.538, chloroform). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1720 (ester), 1657 (amide). NMR (in $CDCl_3$): 1.30 (3H, t, $J$=7 Hz, $C\underline{H}_3CH_2$), 1.57—2.47 (4H, m, $C\underline{H}_2C\underline{H}_2CH_2N$), 2.47—3.27 (4H, m, $C\underline{H}_2C\underline{H}_2C$=), 3.77 (2H, t, $J$=6 Hz, $C\underline{H}_2N$), 4.22 (2H, q, $J$=7 Hz, $CH_3C\underline{H}_2$), 4.42—4.54 (1H, NC$\underline{H}$CO), 7.17 (1H, br s, C$\underline{H}$=), 7.70 (2H, m, aromatic protons), 8.15 (2H, m, aromatic protons). *Anal.* Calcd. for $C_{28}H_{27}NO_7$–$H_2O$: C, 66.26; H, 5.76; N, 2.76. Found: C, 66.49; H, 5.38; N, 2.77.

**(*S*)(—)-N-(5,8-Dimethoxy-3,4-dihydro-2-naphthoyl)proline** ((*S*)-**17b**)——Hydrolysis of (*S*)-**16b** ($[\alpha]_D^{20}$ −10.3° ($c$=2.28, ethanol)) (8.20 g, 21.5 mmol) in the same way as (*S*)-**16a** gave crude (*S*)-**17b** as colorless pillars (7.4 g, 97%), mp 194—198°, $[\alpha]_D^{20}$ −3.0° ($c$=3.24, 2 N NaOH), after concentration of the combined ethyl acetate extracts *in vacuo*. Recrystallization of this sample from ethanol gave pure (*S*)-**17b** as colorless pillars, mp 198—200°, $[\alpha]_D^{20}$ −3.0° ($c$=3.01, 2 N NaOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1730 (acid), 1630 (amide). NMR (in $CDCl_3$–DMSO-$d_6$): 1.67—2.97 (8H, m, $C\underline{H}_2C\underline{H}_2C$= and $C\underline{H}_2C\underline{H}_2CH_2N$), 3.37—4.97 (2H, m, $C\underline{H}_2N$), 3.76 (6H, s, two $OC\underline{H}_3$), 4.17—4.57 (1H, m, NC$\underline{H}$CO), 6.73 (1H, d, $J$=10.7 Hz, one of the aromatic protons), 6.82 (1H, d, $J$=10.7 Hz, one of the aromatic protons), 7.14 (1H, br s, C$\underline{H}$=). *Anal.* Calcd. for $C_{18}H_{21}NO_5$; C, 65.24; H, 6.39; N, 4.23. Found: C, 65.12; H, 6.56; N, 4.35.

**(*S*)(—)-N-(5,12-Dimethoxy-6,11-dioxo-3,4,6,11-tetrahydronaphthacene-2-carbonyl)proline** ((*S*)-**17c**)——Hydrolysis of (*S*)-**16c** ($[\alpha]_D^{20}$ −14.4° ($c$=0.560, chloroform)) (1.70 g, 3.47 mmol) as described for (*S*)-**16a** gave almost pure (*S*)-**17c** as a yellow oil (1.43 g, 89%), $[\alpha]_D^{20}$ −30.4° ($c$=1.40, benzene), on concentration of the combined ethyl acetate extracts. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1730 (acid), 1660 (quinone). NMR (in $CDCl_3$–DMSO-$d_6$): 1.77—2.47 (4H, m, $C\underline{H}_2C\underline{H}_2CH_2N$), 2.47—3.27 (4H, m, $C\underline{H}_2C\underline{H}_2C$=), 3.57—4.07 (2H, m, $C\underline{H}_2N$), 3.80 (3H, s, $OC\underline{H}_3$), 4.13 (3H, s, $OC\underline{H}_3$), 4.47—4.87 (1H, m, NC$\underline{H}$CO), 7.22 (1H, br s, C$\underline{H}$=), 7.45 (1H, br s, COO$\underline{H}$), 7.78 (2H, m, aromatic protons), 8.14 (2H, m, aromatic protons).

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**5,8-Dimethoxy-1′,4′-dioxo-3,4,6′,7′,8′,8′a-(*S*)hexahydrospiro[naphthalene-2(*R*)(1H),3′(*R*)(4′H)-1H-pyrrolo[2,1-c][1,4]oxazine] (19Ab) and Its 2(S),3′(S)-Isomer (19Bb)**——a) Bromolactonization Reaction of (*S*)-**17b**: Treatment of (*S*)-**17b** ($[\alpha]_D^{20}$ −3.0° (*c*=3.24, 2 N NaOH)) (5.00 g, 15.1 mmol) as described for (*S*)-**17a** gave crude unstable **18b** (**18Ab**: **18Bb** 98.5: 1.5) (*vide infra*) as a pale red oil (5.44 g, 87%) after concentration of the combined ethyl acetate extracts *in vacuo*. Purification of a part of the crude **18b** (150 mg) on a short silica gel column (hexane–ether 1: 4) gave almost pure **18b** (a mixture of **18Ab** and **18Bb**) as a pale yellow oil (130 mg), $[\alpha]_D^{20}$ +36.0° (*c*=1.38, chloroform). IR $\nu_{max}^{film}$ $cm^{-1}$: 1760 (lactone), 1672 (amide). NMR (in $CDCl_3$): 1.56—2.86 (6H, $CH_2C\underline{H}_2CCHBr$ and $C\underline{H}_2C\underline{H}_2CH_2N$), 2.86—3.26 (2H, m, $C\underline{H}_2CH_2CCHBr$), 3.36—3.96 (2H, m, $C\underline{H}_2N$), 4.26—4.76 (1H, m, $NC\underline{H}CO$), 3.76 (3H, s, $OC\underline{H}_3$), 3.81 (3H, s, $OC\underline{H}_3$), 5.56 (1H, d, *J*=1.7 Hz, $C\underline{H}Br$),[44] 6.62 (1H, d, *J*=10.2 Hz, one of the aromatic protons), 6.72 (1H, d, *J*=10.2 Hz, one of the aromatic protons). This unstable bromolactone (**18b**) was immediately used for the next debromination reaction.

b) Debromination Reaction of **18b**: Treatment of crude **18b** (5.24 g, 12.7 mmol) as described for crude **18a** gave crude **19b** (a mixture of **19Ab** and **19Bb**) as colorless needles (4.01 g, 95%), mp 169—174°, $[\alpha]_D^{20}$ −138° (*c*=0.368, chloroform), after purification by column chromatography (silica gel, using first hexane, then hexane–ether 1: 1, and finally ether–ethyl acetate 4: 1). A part of this sample (2.69 g) was recrystallized from ether–chloroform to give pure **19Ab** as colorless needles (2.17 g, 81% recovery), mp 187—188°, $[\alpha]_D^{20}$ −152° (*c*=0.424, chloroform). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1748 (lactone), 1650 (amide). NMR (in $CDCl_3$): 1.64—2.69 (6H, m, $CH_2C\underline{H}_2CCH_2$ and $C\underline{H}_2C\underline{H}_2CH_2N$), 2.69—3.29 (4H, m, $C\underline{H}_2CH_2CC\underline{H}_2$), 3.29—3.84 (2H, m, $C\underline{H}_2N$), 3.71 (3H, s, $OC\underline{H}_3$), 3.76 (3H, s, $OC\underline{H}_3$), 4.24—4.64 (1H, m, $NC\underline{H}CO$), 6.54 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.94; H, 6.33; N, 4.31.

**5,12-Dimethoxy-1′,4′,6,11-tetraoxo-3,4,6,6′,7′,8′,8′a(*S*),11-octahydro-spiro[naphthacene-2(*R*)(1H),3′(*R*)-(4′H)-1H-pyrrolo[2,1-*c*][1,4]oxazine](19Ac) and Its 2(*S*),3′(*S*)-Isomer (19Bc)**——a) Bromolactonization Reaction of (*S*)-**17c**: Treatment of (*S*)-**17c** ($[\alpha]_D^{20}$ −30.4° (*c*=1.40, benzene)) (1.14 g, 2.46 mmol) as described for (*S*)-**17a** gave crude extremely unstable **18c** (**18Ac**: **18Bc** 93.5: 6.5) (*vide infra*) as a reddish yellow oil (1.41 g, quantitative yield) after concentration of the combined ethyl acetate extracts. This sample was immediately used for the next debromination reaction.

b) Debromination Reaction of **18c**: Treatment of crude **18c** (1.41 g, 2.61 mmol) as described for crude **18a** gave crude **19c** (a mixture of **19Ac** and **19Bc**) as a yellow solid (570 mg, 50% from (*S*)-**17c**), mp 205—212°, $[\alpha]_D^{20}$ ±0° (*c*=0.21, chloroform), after purification by column chromatography (silica gel, using first ether, then ether–ethyl acetate 2: 7). A part of the crude **19c** (24 mg) was recrystallized from chloroform–ether, giving pure **19Ac** as a yellow powder (13 mg, 54% recovery), mp 214—215°, $[\alpha]_D^{20}$ +11.9° (*c*=0.216, chloroform). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1743 (lactone), 1665 (quinone), 1645 (amide). NMR (in $CDCl_3$): 1.85—2.65 (6H, m, $CH_2C\underline{H}_2CCH_2$ and $C\underline{H}_2C\underline{H}_2CH_2N$), 2.80—3.55 (4H, m, $C\underline{H}_2CH_2CC\underline{H}_2$), 3.75—4.25 (2H, m, $C\underline{H}_2N$), 3.85 (3H, s, $OC\underline{H}_3$), 3.95 (3H, s, $OC\underline{H}_3$), 4.25—4.65 (1H, m, $NC\underline{H}CO$), 7.63 (2H, m, aromatic protons), 8.18 (2H, m, aromatic protons). *Anal.* Calcd. for $C_{26}H_{23}NO_7$: C, 67.67; H, 5.02; N, 3.04. Found: C, 67.69; H, 4.98; N, 2.95.

**(*R*)(—)-Methyl 2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate ((*R*)-21b)**——A mixture of **19Ab** (mp 186—188°, $[\alpha]_D^{20}$ −152° (*c*=0.424, chloroform)) (1.47 g, 4.44 mmol) and 7.5 N HCl (66 ml) in methanol (66 ml) was heated under reflux for 8 hr, then concentrated *in vacuo* to one-third of the original volume. The acidic aqueous solution was saturated with NaCl, and extracted with ethyl acetate. The combined organic extracts were washed with $H_2O$ and satd. NaCl. Filtration and concentration *in vacuo* gave a mixture of (*R*)-**12b** and (*R*)-**21b** as a dark colored oil which was dissolved in methanol. Addition of excess ethereal diazomethane solution to the methanolic solution, followed by concentration *in vacuo*, afforded crude (*R*)-**21b** as a pale yellow oil (1.02 g, 87%). Purification of crude (*R*)-**21b** by column chromatography (silica gel, using hexane–ether 1: 2) gave optically pure (*R*)-**21b** in a pure state (907 mg, 77%), a colorless oil. $[\alpha]_D^{20}$ −34.5° (*c*=1.69, chloroform). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3520 (OH), 1730 (ester). NMR (in $CDCl_3$): 1.99 (2H, br t, *J*=6.5 Hz, $CH_2C\underline{H}_2CCH_2$), 2.53—3.23 (4H, , $C\underline{H}_2CH_2CC\underline{H}_2$), 2.96 (1H, s, $O\underline{H}$), 3.78 (3H, s, $OC\underline{H}_3$), 3.80 (3H, s, $OC\underline{H}_3$), 3.83 (3H, s, $CO_2C\underline{H}_3$), 6.64 (2H, s, aromatic protons). MS: *m/e*: 266 [$M^+$].

When crude **19b** (a mixture of **19Ab** and **19Bb**) (mp 169—174°, $[\alpha]_D^{20}$ −138° (*c*=0.368, chloroform)) (447 mg, 1.35 mmol) was treated as described above, partially optically active (*R*)-**21b**, $[\alpha]_D^{20}$ −33.3° (*c*=1.76, chloroform), was obtained as a colorless oil (248 mg, 69%). The spectral (IR and NMR) properties of this sample were identical with those of optically pure (*R*)-**21b**. Since the optical purity of (*R*)-**21b** thus obtained was calculated as 97%, the formation ratio of **18Ab** and **18Bb** was 98.5: 1.5.

**(*R*)(—)-Methyl 2-Hydroxy-5,12-dimethoxy-6,11-dioxo-1,2,3,4,6,11-hexahydronaphthacene-2-carboxylate ((*R*)-21c)**——HCl (36%, 72 ml) was added to a dioxane solution (18 ml) of crude **19c** (a mixture of **19Ac** and **19Bc**) ($[\alpha]_D^{20}$ ±0° (*c*=0.210, chloroform)) (352 mg, 0.76 mmol), and the mixture was heated under reflux under a nitrogen atmosphere for 7 hr. After cooling in an ice-bath for 30 min, (*R*)-**12d** crystallized out as a red powder, and was collected by filtration. A solution of (*R*)-**12d** in a mixture of DMSO (4 ml) and methanol (14 ml) was treated with an ethereal solution of diazomethane until the evolution of nitrogen gas ceased. Concentration of the reaction mixture *in vacuo* gave a residue, which was dissolved in ethyl acetate. The ethyl acetate solution was washed successively with $H_2O$ and satd. NaCl. Filtration and concentration *in vacuo* gave (*R*)-**21d** as a red powder, which was subjected to methylation of the phenolic hydroxy groups.

44) This signal might couple with one of the C-3 protons. See footnote 43.

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Anhyd. $K_2CO_3$ (378 mg, 2.74 mmol) and dimethyl sulfate (314 mg, 2.49 mmol) were added to a solution of (*R*)-**21d** in acetone (30 ml), and the acetone suspension was heated under reflux for 6 hr under a nitrogen atmosphere. The reaction mixture was filtered, and the insoluble materials collected were washed with acetone. The combined filtrates and washings were concentrated *in vacuo*, and the evaporation residue was dissolved in ethyl acetate (150 ml). The ethyl acetate solution was washed successively with satd. $NaHCO_3$, $H_2O$, and satd. NaCl. Filtration and concentration *in vacuo* gave crude (*R*)-**21c** as a red oil (420 mg). This was subjected to column chromatography (silica gel, solvent ether) to afford partially optically active (*R*)-**21c** in a pure state (261 mg, 87% from **19c**), yellow powder, mp 148—153°, $[\alpha]_D^{20}$ −6.8° ($c$=0.590, acetone). The spectral (IR and NMR) properties of this sample were identical with those of optically pure (*R*)-**21c** prepared as described below.

A part of the partially optically active (*R*)-**21c** (73 mg) was purified by preparative tlc (silica gel, solvent ether) then recrystallization from hexane–ether, giving (*R*)-**21c** as pale yellow needles (54 mg, 74% recovery), mp 154—155°, $[\alpha]_D^{20}$ −7.8° ($c$=0.613, acetone). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400 (OH), 1702 (ester), 1660 (quinone). NMR (in $CDCl_3$): 1.87—2.27 (2H, m, $CH_2C\underline{H}_2CCH_2$), 2.87—3.37 (4H, m, $C\underline{H}_2CH_2CC\underline{H}_2$), 3.17 (1H, s, O<u>H</u>), 3.86 (3H, s, $CO_2C\underline{H}_3$), 3.90 (3H, s, $OC\underline{H}_3$), 3.92 (3H, s, $OC\underline{H}_3$), 7.69 (2H, m, aromatic protons), 8.12 (2H, m, aromatic protons). *Anal.* Calcd. for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.35; H, 5.06. Since purified (*R*)-**21c** can be assumed to be optically pure, the optical purity of partially optically active (*R*)-**21c** can be calculated as 87%. Accordingly, the formation ratio of **18Ac** and **18Bc** was 93.5: 6.5.

**(*R*)(—)-2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid ((*R*)-12b)**——An aqueous solution (8 ml) of KOH (85% pure) (279 mg, 4.23 mmol) was added to a methanolic solution (8 ml) of optically pure (*R*)-**21b** ($[\alpha]_D^{20}$ −34.5° ($c$=1.69, chloroform)) (820 mg, 3.08 mmol), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated *in vacuo* to one-half of the original volume, then washed with ethyl acetate after dilution with satd. NaCl. The alkaline solution was acidified (pH≒2) with conc. HCl saturated with NaCl, and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with satd. NaCl. Filtration and evaporation *in vacuo* gave optically pure (*R*)-**12b** in an almost pure state (740 mg, 96%), pale blue pillars, mp 117—120°, $[\alpha]_D^{20}$ −37.9° ($c$=1.01, chloroform). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3600—3200 (OH), 1710 (acid). NMR (in $CDCl_3$): 1.84—2.24 (2H, br t, $J$=6 Hz, $CH_2C\underline{H}_2CCH_2$), 2.64—3.24 (4H, m, $C\underline{H}_2CH_2CC\underline{H}_2$), 3.78 (3H, s, $OC\underline{H}_3$), 3.80 (3H, s, $OC\underline{H}_3$), 6.44 (2H, br s, O<u>H</u> and COO<u>H</u>), 6.44 (2H, s, aromatic protons), 6.54 (2H, s, aromatic protons). Recrystallization from hexane–ether gave an analytical sample of (*R*)-**12b** as the monohydrate, colorless pillars, mp 91—93°, $[\alpha]_D^{20}$ −39.3° ($c$=0.353, chloroform). *Anal.* Calcd. for $C_{13}H_{16}O_5$–$H_2O$: C, 57.77; H, 6.71. Found: C, 58.10; H, 6.74.

**(*R*)(+)-1-Hydroxy-5,12-dimethoxy-6,11-dioxo-1,2,3,4,6,11-hexahydronaphthacene-2-carboxylic Acid ((*R*)-12c)**——Treatment of optically pure (*R*)-**21c** ($[\alpha]_D^{20}$ −7.8° ($c$=0.613, acetone)) (50 mg, 0.118 mmol) as described for (*R*)-**21b** gave optically pure (*R*)-**12c** as a yellow solid (48 mg, quantitative yield) after concentration of the combined ethyl acetate extracts. Recrystallization of this sample from hexane–ethyl acetate gave an analytical sample of optically pure (*R*)-**12c** as a yellow powder (35 mg), mp 200—201°, $[\alpha]_D^{20}$ +13.6° ($c$=0.430, chloroform). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3480 (OH), 1723 (acid), 1655, 1650 (quinone). NMR (in $CDCl_3$–DMSO-$d_6$): 1.80—2.25 (2H, m, $CH_2C\underline{H}_2CCH_2$), 2.75—3.35 (4H, m, $C\underline{H}_2CH_2CC\underline{H}_2$), 3.90 (6H, s, two $OC\underline{H}_3$), 7.75 (2H, m, aromatic protons), 8.15 (2H, m, aromatic protons). *Anal.* Calcd. for $C_{22}H_{20}O_7$–1/4$H_2O$: C, 65.19; H, 4.82. Found: C, 65.28; H, 4.77.

**(*R*)(—)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-9b) and (R)-2-(1-Hydroxy-1-methyl)-ethyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol[40] ((*R*)-20b)**——Treatment of optically pure (*R*)-**12b** (mp 117—120°, $[\alpha]_D^{20}$ −37.9° ($c$=1.01, chloroform)) (670 mg, 2.66 mmol) as described for (*R*)-**12a** afforded optically pure (*R*)-**9b** as pale yellow needles (420 mg, 63%), mp 119—126°, $[\alpha]_D^{20}$ −47.4° ($c$=1.06, chloroform), and optically pure (*R*)-**20b** as a colorless oil (182 mg, 26%) after separation by column chromatography (silica gel, using hexane–ether 1: 4).

Recrystallization of optically pure (*R*)-**9b** from chloroform-ether gave an analytical sample as colorless needles, mp 128—129°, $[\alpha]_D^{20}$ −48.2° ($c$=0.982, chloroform) (lit.,[23] mp 130—132°, $[\alpha]_D^{20}$ −50° ($c$=1, chloroform)). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3480 (OH), 1700 (ketone). NMR (in $CDCl_3$): 1.87 (2H, br t, $J$=6.5 Hz, $CH_2$-$C\underline{H}_2CCH_2$), 2.29 (3H, s, $COC\underline{H}_3$), 2.52—3.02 (4H, m, $C\underline{H}_2CH_2CC\underline{H}_2$), 3.52 (1H, s, O<u>H</u>), 3.76 (3H, s, $OC\underline{H}_3$), 3.78 (3H, s, $OC\underline{H}_3$), 6.62 (2H, s, aromatic protons). These spectra were identical with those reported for the racemic compound.[10a,12] *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.40; H, 7.26.

The (*R*)-alcohol ((*R*)-**20b**) formed as a by-product had the following spectral properties. IR $\nu_{max}^{film}$ $cm^{-1}$: 3460 (OH). NMR (in $CDCl_3$): 1.30 (3H, s, $C\underline{H}_3$), 1.34 (3H, s, $C\underline{H}_3$), 1.10—2.40 (2H, m, $CH_2C\underline{H}_2CCH_2$), 1.91 (1H, s, O<u>H</u>), 2.20 (1H, s, O<u>H</u>), 2.50—3.00 (4H, m, $C\underline{H}_2CH_2CC\underline{H}_2$), 3.77 (3H, s, $OC\underline{H}_3$), 3.79 (3H, s, $OC\underline{H}_3$), 6.64 (2H, s, aromatic protons).

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