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ASYMMETRIC PHOTOCYCLIZATIONS OF CHIRAL AUXILIARY-SUBSTITUTED *N*-ACYL-α-DEHYDROAMINO ACIDS INTO 1,2-DIHYDROBENZOQUINOLINONE DERIVATIVES

Kei Maekawa,* Tetsutaro Igarashi, Kanji Kubo,† and Tadamitsu Sakurai*

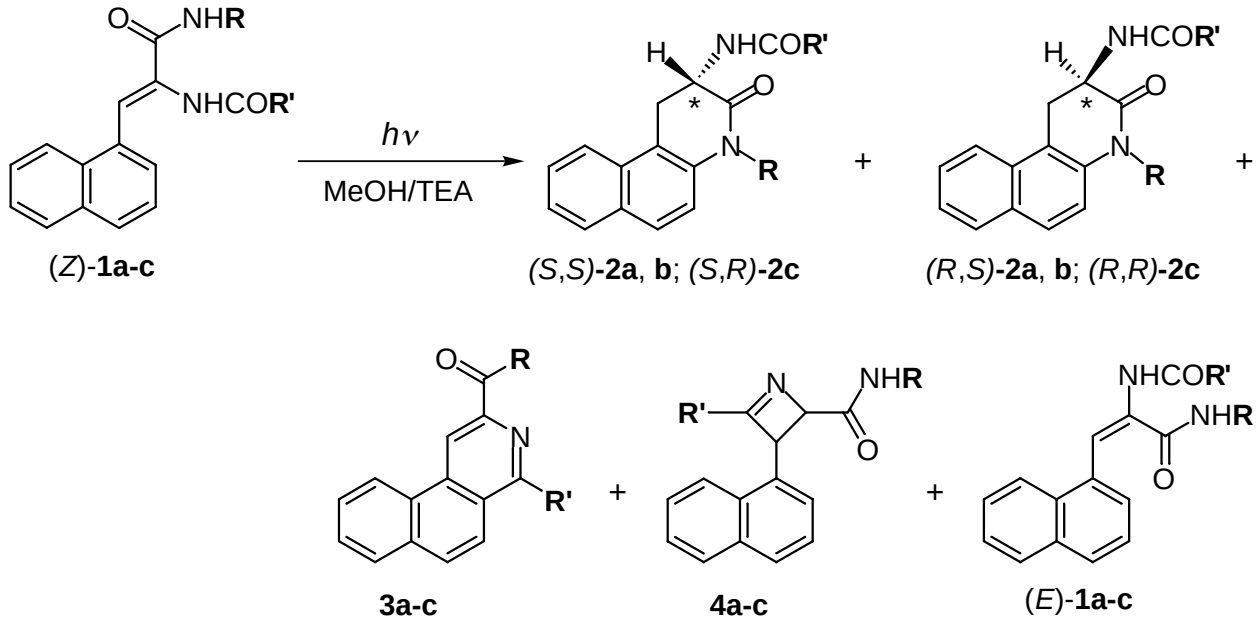
Department of Applied Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686, Japan
†Institute of Advanced Material Study, 86, Kyushu University, Kasuga-Koen, Kasuga, Fukuoka 816-0811, Japan

Abstract—The irradiation of the title compounds [(*Z*)-**1**] with an (*S*)-alanine auxiliary in methanol containing a tertiary amine afforded a diastereomeric mixture of (*S,S*)- and (*R,S*)-1,2-dihydrobenzo[*f*]quinolinones, along with (*E*)-**1**, benzo[*f*]isoquinoline, and 1-azetine derivatives. It was found that electron transfer-initiated photocyclizations of (*Z*)-**1** in polar solvents give (*S,S*)-1,2-dihydrobenzoquinolinones in diastereomeric excess whose value varies from 0 to 55% depending on the properties of the amine and solvent employed.

Organic photochemistry has continued to contribute to the developement of efficient and selective transformations for the preparation of complicated molecules which could not have been synthesized by conventional methods.[1] Thus far, much attention has been given to developing novel asymmetric reactions utilizing photocyclizations and photoadditions of organic compounds in liquid and solid phases.[2,3] However, there are only a few photoreactions that afford cyclized products in high enantio- and diastereoselectivities, especially in liquid phase.[2] Very recently, we found that 1-naphthyl-substituted *N*-acyl-α-dehydroamino acids (**1**) in methanol containing triethylamine (TEA) undergo electron transfer (ET)-initiated photocyclizations giving racemic 1,2-dihydrobenzo[*f*]quinolinones (**2**).[4] Thus, the incorporation of a chiral auxiliary into the starting (*Z*)-**1** makes it possible to develope novel asymmetric photoreactions in liquid phase and then to shed some light on the mechanism of ET-initiated photocyclizations found by us. For these ends we synthesized (*Z*)-*N*-acyl-α-dehydroamino acid derivatives [(*Z*)-**1a**–**c**] having the (*S*)- or (*R*)-alanine auxiliary and investigated the effects of chiral auxiliary, tertiary amine, and solvent on the magnitude of diastereomeric excess (de).

The starting (*Z*)-**1a**–**c** were prepared in excellent yields by the ring-opening reactions of (*Z*)-1-naphthyl-substituted oxazolones with (*S*)-alanine (**1a**,**b**) or (*R*)-alanine (**1c**) methyl ester.[5] After a nitrogen-purged methanol solution of (*Z*)-**1a** (3.75×10^{-3} mol dm^{-3}) containing TEA (0.10 mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 450 W high-pressure Hg lamp for 5 h at room temperature, the

product mixture obtained was subjected to column chromatography over silica gel, which allowed us to isolate the starting (*Z*)-**1a** (8.1%, isolated yield), (*E*)-**1a** (4.0%), a mixture of (*S*,*S*)-**2a** and (*R*,*S*)-**2a** (32.9%), and benzo[*f*]isoquinoline derivative (**3a**) (21.8%) (Scheme 1).[6]



1a (**R**= (*S*)-*CH(Me)CO_2Me, **R'**= Me); **1b** (**R**= (*S*)-*CH(Me)CO_2Me, **R'**= Ph)
1c (**R**= (*R*)-*CH(Me)CO_2Me, **R'**= Me)

Scheme 1

Table 1. Relation between irradiation time and composition (%) of each compound obtained by the irradiation of (*Z*)-**1a** in MeOH–TEA at room temperature

Compound	Irradiation time (h)							
	0	0.5	1.0	1.5	2.0	3.0	4.0	5.0
(*Z*)-**1a**	100	56.4	43.2	37.9	33.2	24.9	16.6	9.4
(*E*)-**1a**	0	39.7	46.1	44.2	38.8	29.6	19.6	12.1
2a[a)]	0	0.7	4.1	7.2	13.4	22.3	31.2	38.4
3a	0	3.1	5.4	8.2	10.9	16.9	23.1	28.3
4a[a)]	0	0	1.2	2.6	2.7	6.2	9.4	12.0

[a)] The mixture of the corresponding diastereomer.

The structures of isolated products were determined based on their spectroscopic and physical properties and were confirmed by the ^{1}H-^{1}H and ^{13}C-^{1}H COSY spectra of these products. However, any attempts to

isolate each diastereomer of 1-azetine derivative (**4a**) were not successful owing to its poor yield, as can be seen from the time-course of the respective product composition monitored by ^{1}H NMR spectroscopy (Table 1). The same product distribution was obtained also by the irradiation of (*Z*)-**1b** and the diastereomeric mixture of (*S*,*S*)-**2a**,**b** and (*R*,*S*)-**2a**,**b** could be separated by repeated preparative TLC (silica gel). An X-Ray structural analysis of single crystal derived from the diastereomer of **2b** (showing its methine proton signal in the chiral auxiliary at 5.16 ppm) revealed that the asymmetric carbon in the dihydroquinolinone ring has the (*R*)-configuration (Figure 1).[7] Furthermore, a comparison of circular dichroism (CD) spectra of the (*R*,*S*)- and (*S*,*S*)-diastereomers isolated confirmed that the dihydroquinolinone ring having (*R*)- and (*S*)-configurations gives CD bands of positive and negative signs at 250 nm, respectively.[8] Thus, we are able to estimate the magnitude of de from the area ratio of the methine proton signals (detected at 5.26 [(*S*,*S*)-**2a**], 5.35 [(*S*,*S*)-**2b**], 5.04 [(*R*,*S*)-**2a**], and 5.16 ppm [(*R*,*S*)-**2b**]) and the absolute configuration of the asymmetric carbon in the ring is definitely determined by ^{1}H NMR and CD spectral analyses of a given diastereomer.

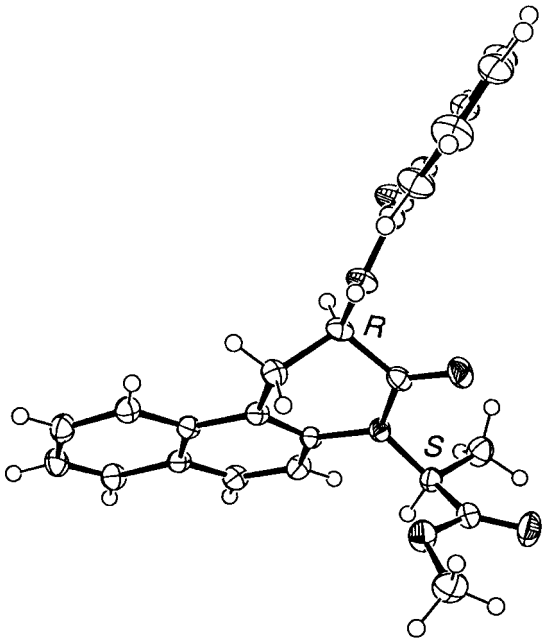


Figure 1. ORTEP drawing of (*R*,*S*)-**2b**

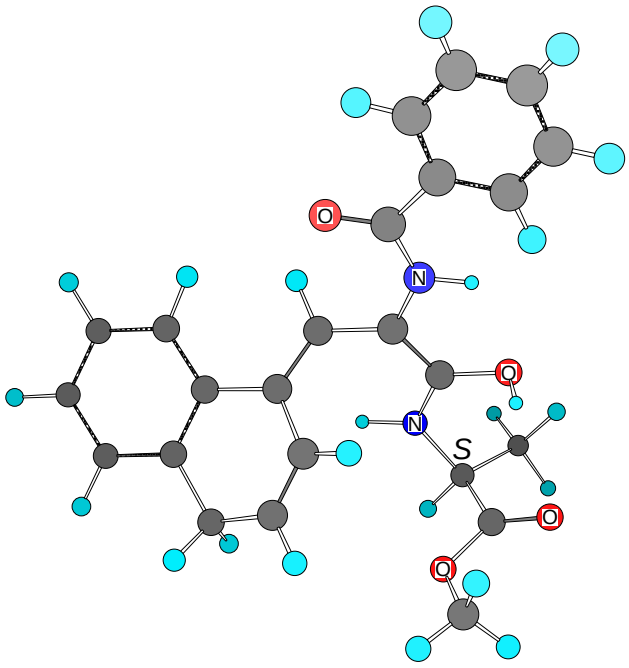


Figure 2. Energy-minimized conformation of **II** (**R'**= Ph)

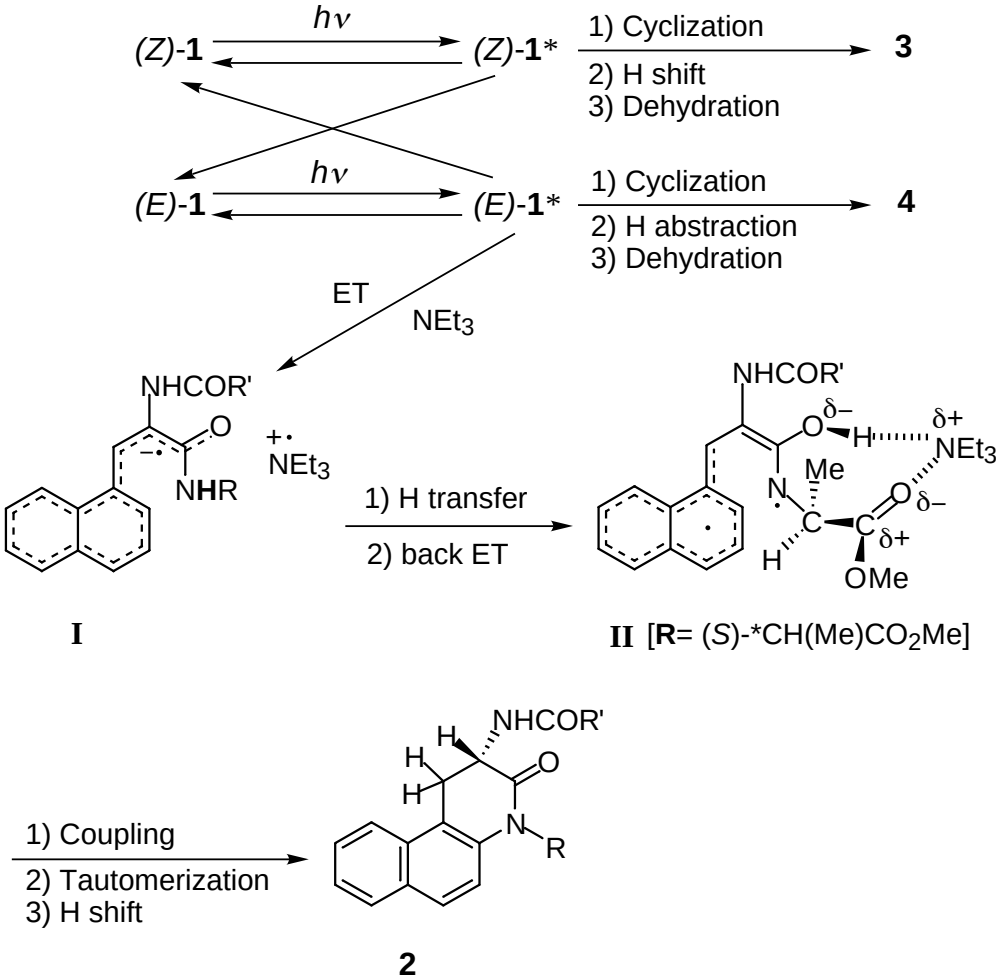
In Table 2 are summarized conversion of (*Z*)-**1**, selectivity for **2**, and % de obtained after the 5 h irradiation in methanol at room temperature. Although steric bulkiness of the chiral auxiliary R lowers the selectivity for **2** as compared to R= Me (88→49%, Table 2),[4] the presence of the (*S*)-alanine auxiliary resulted in a preferential formation of (*S*,*S*)-**2a** (de = 9%). The observation that the irradiation of (*Z*)-**1c** possessing the (*R*)-alanyl group under the same conditions gives preferentially (*R*,*R*)-**2c** in the same de demonstrates the occurrence of asymmetric induction in the cyclization process eventually yielding **2**. It was suggested in the previous study that the asymmetric carbon at the 2-position in the dihydrobenzoquinolinone ring is generated by tautomerization of the enol intermediate (**II**) [formed *via* the radical ion pair (**I**)], as shown in

Scheme 2.[4] Evidence in support of this suggestion comes from the fact that deuterium attached to the alanine auxiliary-substituted amide nitrogen is transferred to the 2-position in the quinolinone ring on irradiation in acetonitrile. An inspection of the ORTEP drawing for (*R*,*S*)-**2b** indicates the ester carbonyl oxygen in the (*S*)-alanyl moiety to be directed preferentially to one of the two diastereofaces and, hence, allows us to expect that there are differences in the extent of hydrogen-bonding and stereoelectronic interactions of TEA with the enol intermediate (**II**) between two diastereofaces. In order to estimate the conformation of (*S*)-alanine auxiliary in **II**, this intermediate structure is approximated by **III** (in which two unpaired electrons are replaced by hydrogen atoms) and is optimized through MM2 calculations (Figure 2). The finding that the conformation of (*S*)-alanine auxiliary is well consistent with that for (*R*,*S*)-**2b** in the solid state strongly suggests that the enol intermediate (**II**) adopts a similar conformation in solution. Accordingly, we are able to provide a good explanation for the observed asymmetric induction by invoking more favorable hydrogen-bonding and stereoelectronic interactions (shown in Scheme 2) in one diastereoface than in the other, which lead to the (*S*,*S*)-diastereomer in a definite de. Asymmetric transformation of (*Z*)-**1b** into (*S*,*S*)-**2b** was achieved in a similar de (Table 2).

Table 2. Chiral auxiliary, tertiary amine and solvent effects on the conversion of (*Z*)-**1**, selectivity of **2**, and diasteremeric excess for (*S*,*S*)-**2** or (*R*,*R*)-**2** obtained by the 5 h irradiation of (*Z*)-**1** (3.75×10^{-3} mol dm^{-3}) at room temperature

(*Z*)-**1**	Tertiary amine	Solvent	Conversion (%)	Selectivity (%)[a]	(*S*,*S*)-**2** (%)[b]	(*R*,*S*)-**2** (%)[b]	de (%)
1a	TEA	MeOH	79	49	54.5	45.5	9
1b	TEA	MeOH	46	45	56.5	43.5	13
1c	TEA	MeOH	79	39	54.5[c]	45.5[d]	9
1a	TMA[e]	MeOH	72	48	59.0	41.0	18
1a	MP[f]	MeOH	74	52	65.5	34.5	31
1a	PEP[g]	MeOH	65	55	50.0	50.0	0
1a	TEA	MeOH-MeCN (1:1 v/v)	82	30	63.0	37.0	26
1a	TEA	MeOH-MeCN (1:9 v/v)	63	9	77.5	22.5	55
1a	MP	MeOH-MeCN (1:9 v/v)	67	13	72.0	28.0	44

[a] Estimated as **2**/(**2**+**3**+**4**). [b] Composition in a mixture of both diastereomers. [c] (*R*,*R*)-**2c**. [d] (*S*,*R*)-**2c**. [e] Trimethylamine. [f] 1-Methylpiperidine. [g] *N*-Isopropyl-*N*-ethylisopropylamine.



Scheme 2

It is very likely that TEA as an electron donor continues to exist in the very vicinity of a given substrate during the photocyclization process. Scheme 2 allows us to predict that the magnitude of de for (*S,S*)-**2a** strongly depends on the steric bulkiness about the tertiary amino nitrogen, namely, a decrease in this bulkiness results in an enhanced de by strengthening the hydrogen-bonding and electrostatic interactions described above and an increase in the bulkiness gives the reverse result. As evident from Table 2, the de value is increased in the following order: PEP<<TEA<TMA<MP. This result is consistent with our prediction and, thus, substantiates the mechanism for the observed asymmetric photoinduction.

If we consider hydrogen-bonding solvation of both the tertiary amines and the intermediate (**II**) in methanol, the use of acetonitrile as a co-solvent may suppress these solvation and thereby enhances hydrogen-bonding and electrostatic interactions between the tertiary amino nitrogen and this intermediate to result in a net increase in de for (*S,S*)-**2**. In Table 2 are collected the results obtained for the (*Z*)-**1a**–TEA and (*Z*)-**1a**–MP systems. As expected, the de value increases with an increase in concentration of the aprotic polar solvent, thus providing additional proof of the mechanism for asymmetric photoinduction in our systems.

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6. Selected data for (*Z*)-**1a**: mp 149.0–150.0 ℃ (EtOAc); IR (KBr): ν/cm^{-1}= 3220, 3052, 2986, 2950, 1746, 1650, 1632; $[\alpha]_D$ +47.3° (c= 0.5, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ=1.37 (3H, d, *J*= 6.7 Hz), 1.83 (3H, s), 3.66 (3H, s), 4.44 (1H, dq, *J*= 6.7, 6.7 Hz), 7.60–7.51 (5H, m), 7.90 (1H, d, *J*= 7.9 Hz), 7.96–7.94 (2H, m), 8.47 (1H, d, *J*= 6.7 Hz), 9.25 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6): δ= 16.9, 22.7, 48.2, 51.9, 124.2, 124.6, 125.5, 126.1, 126.3, 126.4, 128.5 (2C), 131.0, 131.3, 132.0, 133.2, 164.9, 169.4, 173.1. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.10; H, 6.04; N, 8.12.

   Data for (*E*)-**1a**: mp 102.0–103.0 ℃ (EtOAc-hexane); IR (KBr): ν/cm^{-1}= 3276, 3048, 2952, 1740, 1678, 1626; $[\alpha]_D$ –46.4° (c= 0.5, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ= 1.05 (3H, d, *J*= 6.7 Hz), 2.03 (3H, s), 3.51 (3H, s), 4.26 (1H, dq, *J*= 6.7, 7.3 Hz), 7.40 (1H, dd, *J*= 7.3, 8.6 Hz), 7.44 (1H, d, *J*= 7.3 Hz), 7.46 (1H, s), 7.52 (1H, dd, *J*= 6.7, 7.9 Hz), 7.55 (1H, dd, *J*= 6.7, 7.3 Hz), 7.80 (1H, d, *J*= 8.6 Hz), 7.91 (1H, d, *J*= 7.9 Hz), 8.00 (1H, d, *J*= 7.3 Hz), 8.30 (1H, d, *J*= 7.3 Hz), 9.74 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6): δ= 16.4, 23.4, 47.4, 51.7, 114.0, 124.4, 125.4, 125.7, 125.9, 126.0, 127.1, 128.2, 131.2, 132.0, 133.0, 133.8, 164.1, 168.5, 172.3. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.04; H, 6.06; N, 8.48.

   Data for (*S,S*)-**2a**: mp 86.0–89.0 ℃ (EtOAc-hexane); IR (KBr): ν/cm^{-1}= 3316, 3064, 2986, 2950, 1746, 1659, 1635; $[\alpha]_D$ +35.2° (c= 0.5, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ= 1.49 (3H, d, *J*=

6.7 Hz), 1.92 (3H, s), 3.01 (1H, dd, *J*= 15.9, 15.3 Hz), 3.60 (1H, dd, *J*= 15.3, 5.5 Hz), 3.60 (3H, s), 4.51 (1H, ddd, *J*= 15.9, 7.9, 5.5 Hz), 5.26 (1H, q, *J*= 6.7 Hz), 7.45 (1H, dd, *J*= 8.3, 7.3 Hz), 7.53 (1H, d, *J*= 9.2 Hz), 7.56 (1H, dd, *J*= 8.6, 7.3 Hz), 7.90 (1H, d, *J*= 9.2 Hz), 7.90 (1H, d, *J*= 8.3 Hz), 8.01 (1H, d, *J*= 8.6 Hz), 8.37 (1H, d, *J*= 7.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ= 15.1, 22.6, 27.1, 48.2, 52.1, 53.6, 116.2, 119.1, 123.3, 124.9, 127.2, 128.2, 128.3, 129.9, 130.7, 136.3, 168.3, 169.4, 171.0. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.75; H, 5.71; N, 8.18.

Data for (*R*,*S*)-**2a**: mp 111.0–113.0 ℃ (EtOAc-hexane); IR (KBr): ν/cm^{-1}= 3304, 3052, 2992, 2950, 1743, 1656, 1640; $[\alpha]_D$ –60.0° (c= 0.5, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ= 1.57 (3H, d, *J*= 6.7 Hz), 1.94 (3H, s), 2.96 (1H, dd, *J*= 15.3, 15.3 Hz), 3.62 (3H, s), 3.64 (1H, dd, *J*= 15.3, 6.1 Hz), 4.55 (1H, ddd, *J*= 15.3, 7.9, 6.1 Hz), 5.04 (1H, q, *J*= 6.7 Hz), 7.34 (1H, d, *J*= 8.5 Hz), 7.46 (1H, dd, *J*= 8.5, 6.7 Hz), 7.56 (1H, dd, *J*= 8.5, 6.7 Hz), 7.91 (2H, d, *J*= 8.5 Hz), 8.02 (1H, d, *J*= 8.5 Hz), 8.39 (1H, d, *J*= 7.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ= 14.6, 22.6, 26.2, 48.1, 52.2, 54.0, 116.3, 119.2, 123.3, 124.9, 127.2, 128.3, 128.4, 129.9, 130.6, 136.5, 168.5, 169.5, 170.9. Anal. Calcd for $C_{19}H_{20}N_2O_4$•H_2O: C, 63.68; H, 6.19; N, 7.82. Found: C, 63.95; H, 5.86; N, 7.44.

Data for **3a**: mp 117.0–118.0 ℃ (EtOAc-hexane); IR (KBr): ν/cm^{-1}= 3340, 3040, 2986, 2944, 1743, 1668, 1623; $[\alpha]_D$ –38.4° (c= 0.5, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ= 1.54 (3H, d, *J*= 7.3 Hz), 3.04 (3H, s), 3.72 (3H, s), 4.70 (1H, dq, *J*= 7.3, 7.3 Hz), 7.78–7.86 (2H, m), 8.07–8.18 (3H, m), 8.85–8.93 (1H, m), 9.06–9.13 (2H, m); ^{13}C NMR (125 MHz, DMSO-d_6): δ= 17.3, 22.5, 47.9, 52.1, 113.4, 122.7, 123.7, 126.4, 127.9, 128.6, 128.7, 129.1, 129.7, 132.8, 134.4, 143.5, 157.2, 164.0, 172.8. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.86; N, 8.64. Found: C, 70.62; H, 5.86; N, 8.64.

Spectroscopic, optical and physical properties of the other starting materials and products will be given elsewhere.

7. Crystal data for (*R*,*S*)-**2b**: $C_{24}H_{22}N_2O_4$, f_w= 402.45; colorless prism, 0.23 × 0.20 × 0.20 mm, monoclinic, space group $P2_1$; a= 6.0757(7), b= 19.3406(2), c= 8.5842(1) Å, α= 90, β= 102.961(4), γ= 90°, V= 983.0(2) Å^3; Z= 2; D_{calc}= 1.360 g cm^{-3}; R= 0.0414, $wR(F^2)$= 0.1164.
8. The molar ellipticities of (*S*,*S*)-**2a**, (*R*,*S*)-**2a**, (*S*,*S*)-**2b** and (*R*,*S*)-**2b** at 250 nm are –1440, +1850, –1990 and +2350 deg cm^2 dmol^{-1}, respectively. The mixture of (*S*,*S*)-**2a** and (*R*,*S*)-**2a** was allowed to stand in methanol containing TEA (0.10 mol dm^{-3}) for 24 h at room temperature but the area ratio of the corresponding methine proton signals remained unchanged. Thus, we are led to conclude that no racemization takes place during workup.