Convenient Catalytic Synthesis and Assignment of the Absolute Configuration of Enantiomerically Pure Dihydronaphthalenes and Their Corresponding Epoxides

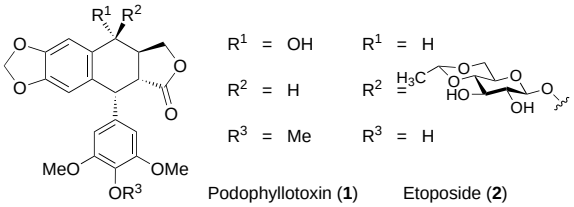
Torsten Linker,* Frank Rebien, Gábor Tóth,* András Simon, Jürgen Kraus, and Gerhard Bringmann*

Abstract: In this paper we report on the synthesis and kinetic resolution of 1,2-dihydronaphthalenes by Jacobsen epoxidation, which proceeds smoothly with good selectivity ($k_{rel} = 6.3 - 9.1$). The yields were conveniently adjusted by variation of the number of equivalents of MCPBA (*m*-chloroperoxybenzoic acid) as the terminal oxidant, to afford enantiomerically pure starting materials or epoxides after one recrystallization. Complete separation of the starting material and the epoxides was effected by HPLC with a chiral stationary phase. Interestingly, the Jacobsen epoxidations afford two diastereomers, whereas the reaction with MCPBA alone proceeds with high diastereoselectivity. This can be attributed to unfavorable steric interactions and a matched–mismatched pair in the transition states. The relative configuration of both diastereomers was elucidated by detailed NMR spectroscopy. Furthermore, the absolute configuration of all the products was established unequivocally by comparison of experimental and calculated circular dichroism (CD) spectra. Since the epoxides can be transformed into the etoposide skeleton in only three steps, the kinetic resolution described herein offers simple access to optically active derivatives of these important anticancer drugs.

Keywords: asymmetric catalysis · circular dichroism · epoxidations · kinetic resolution · quantum-chemical calculations

Introduction

Lignans represent an important class of natural products, which possess interesting biological properties and have become challenging targets for organic synthesis.[1] Owing to their cytostatic properties, podophyllotoxin (**1**) and etoposide (**2**) are currently the most intensively studied of the various derivatives.[2] Furthermore, etoposide exhibits very high antitumor activity and is used for the treatment of many human malignancies.[3] In the course of our continuing interest in selective oxidation reactions,[4] we have developed a short and convenient synthetic route to the etoposide skeleton.[5] Thus, starting from 2-naphthoic acid (**3**), the analogue *rac*-**4** was synthesized in only 11 steps and 35% overall yield. The key step was MCPBA (*m*-chloroperoxybenzoic acid) epoxidation of the dihydronaphthalene derivative *rac*-**5**, which afforded exclusively one diastereomer *rac*-**6a** (Scheme 1).[5a] However, until now, the epoxide (**6a**) was only obtained in racemic form, which represents a drawback for applications requiring the total synthesis of etoposide (**2**).



Podophyllotoxin (**1**) Etoposide (**2**)

Our new approach to this problem is based on catalytic kinetic resolution of the dihydronaphthalenes *rac*-**5**. For this purpose, the Jacobsen–Katsuki epoxidation should be a

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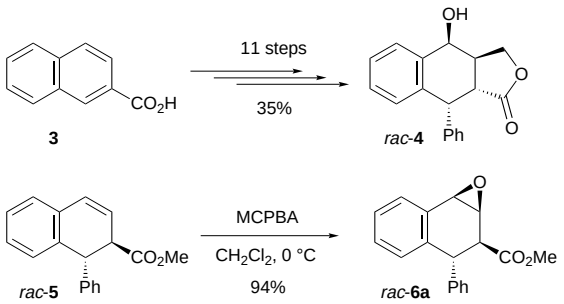
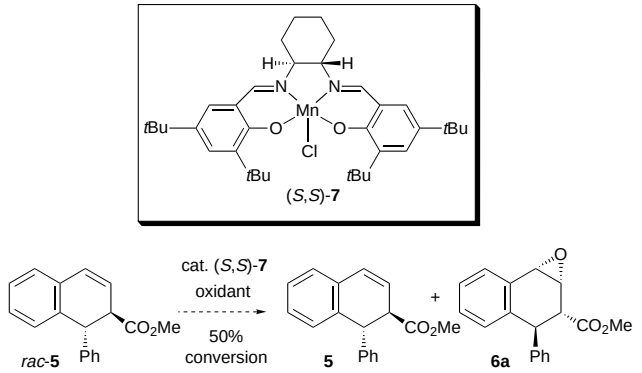


Scheme 1. Synthesis of the racemic etoposide analogue *rac*-**4** and the epoxide *rac*-**6a**.

valuable tool, since it is established as an important method for the formation of asymmetric carbon–oxygen bonds.[6] Thus, by employing the commercially available catalyst (*S*,*S*)-**7** and a terminal oxidant, it should be possible to synthesize the desired dihydronaphthalene **5** in enantiomerically pure form (Scheme 2). However, although numerous

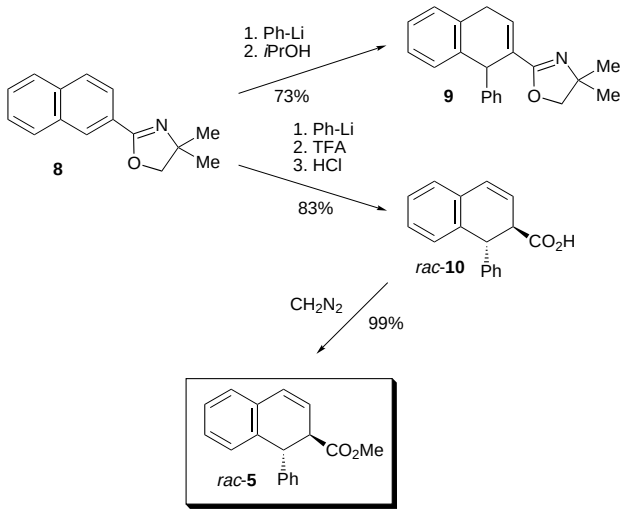


Scheme 2. Strategy for the synthesis of enantiomerically pure products by kinetic resolution with Jacobsen epoxidation.

synthetic applications of the Jacobsen–Katsuki epoxidation have been reported in the literature, only three examples of kinetic resolution by this method have been published hitherto and these afforded only moderate levels of enantiomeric excess (*ee*).[7] Herein we describe the successful synthesis of both the dihydronaphthalene **5** and the epoxide **6a** in enantiomerically pure form by this strategy. Furthermore, the absolute configuration of all the products was established unequivocally by comparison of experimental and quantum-chemically calculated CD spectra.

Results and Discussion

The oxazoline **8** was easily synthesized on a multigram scale from 2-naphthoic acid (**3**) in a one-pot procedure.[8] According to the elegant methodology developed by Meyers,[9] nucleophilic addition of phenyllithium to **8** occurs with very high regioselectivity at the 1-position. However, owing to the isomerization of the double bond under the basic reaction conditions, isopropanol as the proton source affords only the 1,4-dihydronaphthalene derivative **9** in 73% yield (Scheme 3). To overcome this problem, trifluoroacetic acid (TFA) was employed. Indeed, the desired 1,2-dihydronaphthalene derivative *rac*-**10** was isolated diastereoselectively in 83% yield, after cleavage of the oxazoline with HCl. The exclusive formation of the *trans* product can be rationalized in



Scheme 3. Synthesis of the dihydronaphthalenes **9** and *rac*-**5**.

terms of protonation of the nitrogen of the azaenolate intermediate by the hard electrophile and subsequent tautomerization to the thermodynamically more stable product. Finally, reaction of the acid *rac*-**10** with diazomethane affords the corresponding methyl ester *rac*-**5** quantitatively (Scheme 3).

To establish the optimal analytical method for *rac*-**6a**, the 1,2-dihydronaphthalene *rac*-**5** was epoxidized in the presence of MCPBA without the addition of Jacobsen catalyst to obtain the racemic product. The epoxide *rac*-**6a** was isolated as a single diastereomer in 94% yield (Table 1, entry 1).[5a] For the determination of the enantiomeric excesses, HPLC was the method of choice, since the alkene **5** and the epoxide **6a** were conveniently separated on a chiral stationary phase (Chiralcel OD-H, Figure 1a).

The first asymmetric epoxidations were conducted at 0 °C in the presence of the Jacobsen catalyst (*S*,*S*)-**7** and with sodium hypochlorite as the terminal oxidant. A conversion of 24% was achieved with 0.4 equiv of NaOCl, which afforded the epoxide (+)-**6a** in 88% *ee* and the dihydronaphthalene (−)-**5** in 20% *ee* (entry 2). As expected, the corresponding enantiomeric isomers were obtained with the(salen)manganese(III) complex (*R*,*R*)-**7** (entry 3). The resulting selectivity factors of 4.4–5.4[10] are considerably higher than those reported in the literature for sodium hypochlorite ($k_{rel} = 1-2$).[7a]

To improve the selectivities further, Jacobsen epoxidations with *m*-chloroperoxybenzoic acid (MCPBA) as the terminal oxidant were investigated next; this procedure allows experiments to be conducted at lower temperatures.[11] A control experiment at −78 °C demonstrated that without catalyst (entry 4) no epoxidation occurs under the reaction conditions, whereas the reaction proceeds quantitatively at 0 °C with MCPBA (entry 1). Only when 0.04 equiv of (*S*,*S*)-**7** and 1.5–

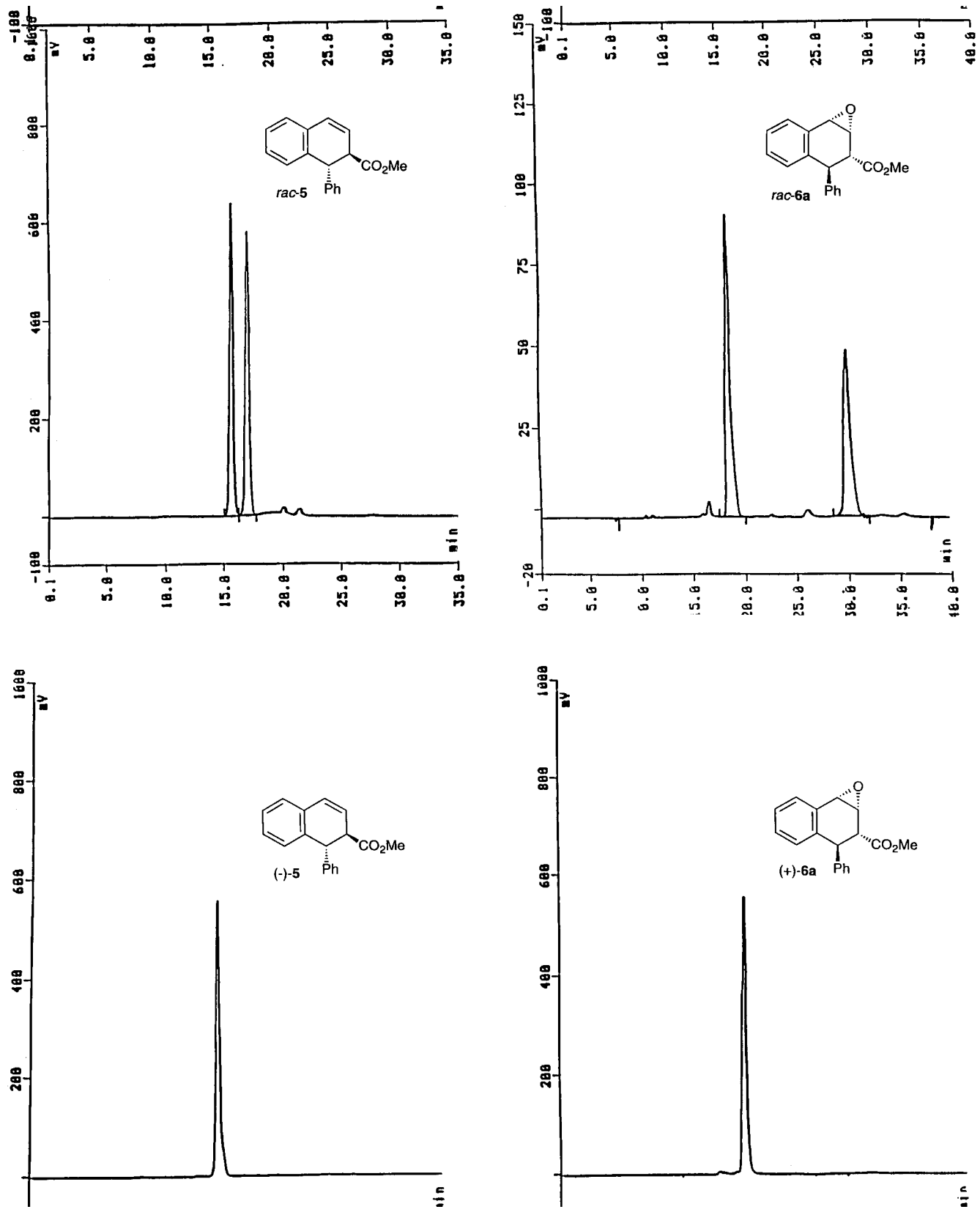


Figure 1. Separation of the dihydronaphthalenes **5** and epoxides **6a** by HPLC on a chiral stationary phase (Chiralcel OD-H); a) racemic mixtures; b) enantiomerically pure compounds.

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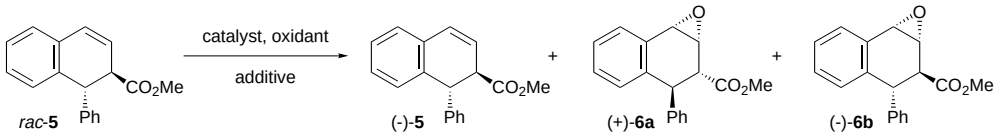
Table 1. Epoxidation of the 1,2-dihydronaphthalenes *rac*-**5**.



Entry	Catalyst [equiv]	Oxidant[a] [equiv]	Additive[b] [equiv]	T [°C]	t [h]	Conv. [%][c]	dr[c] **6a**:**6b**	product distribution [% *ee*][d] (−)-**5**:(+)-**6a**:(−)-**6b**	k_{rel}[10]
1	–	MCPBA [1.2]	–	0	7.0	>98	>98:2	<2 : >96 : <2	–
2	(*S*,*S*)-**7** [0.04]	NaOCl [0.4]	4-PPNO [0.1]	0	2.0	24	87:13	76 : 21 : 3 [20] [88] [e]	5.4
3	(*R*,*R*)-**7**[f] [0.04]	NaOCl [0.4]	4-PPNO [0.1]	0	1.5	34	71:29	66 : 24 : 10 [28] [80] [e]	4.4
4	–	MCPBA [0.9]	NMO [2.2]	−78	3.0	<5	–	–	–
5	(*S*,*S*)-**7** [0.04]	MCPBA [0.6]	NMO [1.5]	−78	1.5	26	77:13	74 : 20 : 6 [26] [93] [e]	8.6
6	(*S*,*S*)-**7** [0.04]	MCPBA [0.8]	NMO [2.0]	−78	1.5	40	60:40	60 : 24 : 16 [47] [91] [e]	9.1
7	(*S*,*S*)-**7** [0.04]	MCPBA [0.9]	NMO [2.2]	−78	1.5	50	72:28	50 : 36 : 14 [57] [87] [e]	6.3
8	(*S*,*S*)-**7** [0.04]	MCPBA [2.0]	NMO [5.0]	−78	2.0	81	54:46	19 : 44 : 37 [>99] [75] [e]	>6.4
9	(*R*,*R*)-**7**[f] [0.04]	MCPBA [0.9]	NMO [2.2]	−78	1.0	52	69:31	48 : 36 : 16 [60] [80] [e]	6.3

[a] *m*-Chloroperoxybenzoic acid (MCPBA) in dichloromethane; NaOCl in phosphate buffer/chlorobenzene. [b] 4-Phenylpyridine-*N*-oxide (4-PPNO) or *N*-methylmorpholine-*N*-oxide (NMO). [c] Determined by ^{1}H NMR analysis of the crude product (200 MHz). [d] Determined by HPLC on chiral stationary phase (Chiralcel-OD-H). [e] No separation by HPLC on a chiral phase was possible. [f] The corresponding enantiomers (+)-**5**, (−)-**6a**, and (+)-**6b** were formed.

2.2 equiv of *N*-methylmorpholine-*N*-oxide (NMO) were added was the epoxide (+)-**6a** isolated in high enantiomeric excess (87–93 % *ee*) at −78 °C (entries 5–7). The conversion was conveniently controlled by variation of the number of equivalents of oxidant. Thus, 2.0 equiv MCPBA yielded at 81 % conversion the dihydronaphthalene (−)-**5** in enantiomerically pure form (entry 8, Figure 1b). Again, the corresponding (salen)manganese(III) complex (*R*,*R*)-**7** afforded the enantiomeric isomers (entry 9). Furthermore, both epoxides (+)-**6a** and (−)-**6a** are available in enantiomerically pure form from one simple recrystallization (Figure 1b). This is an important finding for the controlled synthesis of optically active etoposide analogues. Finally, the higher selectivities achieved with MCPBA (k_{rel} = 6.3–9.1) compared with NaOCl can be attributed to the lower reaction temperature and are unprecedented for kinetic resolutions with catalyst **7**.[7a]

Interestingly, all the Jacobsen epoxidations examined afford diastereomeric mixtures, whereas reactions without catalyst are highly diastereoselective (entry 1). The relative configuration of both epoxides **6a** and **6b** was unequivocally elucidated by detailed one- and two-dimensional ^{1}H and ^{13}C NMR spectroscopy.[12] The important determination of the absolute configuration of all reaction products was achieved by comparison of experimental CD spectra with those obtained from quantum-chemical calculations—an efficient method further developed and improved by our group.[13–15]

Starting with the arbitrarily chosen 1*R*,2*S*,3*S*,4*R* enantiomer of the main product **6a**, conformational analysis using semiempirical methods (AM1[16] and PM3,[17, 18] see section on computational methods) revealed the presence of eight conformers, which differ by three conformational parameters: rotation of the ester *O*-methyl group about the adjacent C–O bond, rotation of the carbonyl oxygen about the neighboring C–C bond, and the conformation of the flexible cyclohexene ring.

For these eight minima, the CD spectra were calculated separately (Figure 2a, left) and summed according to the principles of Boltzmann statistics. The calculated overall spectrum for (1*R*,2*S*,3*S*,4*R*)-**6a** (Figure 2b, left), is almost the reverse of the experimental one, while the spectrum calculated for (1*S*,2*R*,3*R*,4*S*)-**6a** (Figure 2b, right) matches the experimental spectrum well, except for a minor shift of the theoretical CD spectrum by about 12 nm to lower wavelengths. Since the same shift is also observed for the UV spectrum calculated by the same program (not shown), the UV shift can be used to rescale the wavelengths for the calculated CD spectrum. Figure 2c (right) shows the excellent agreement of the experimental CD spectrum with the rescaled,[13] theoretical one for the 1*S*,2*R*,3*R*,4*S* enantiomer. Therefore the 1*S*,2*R*,3*R*,4*S* configuration can be assigned unambiguously to the main epoxide (+)-**6a**. As in previous cases,[15] the calculations are quite independent of the experimental CD spectra and are therefore true theoretical predictions.

Similarly, the absolute configuration of the minor product, epoxide (−)-**6b**, was investigated and found to be 1*R*,2*S*,3*R*,4*S*, with the same absolute configuration in the epoxide part (C-3 and C-4) as the main product (+)-**6a**, but the opposite configuration at the C-1 and C-2 stereocenters. In this case, because of the unusual conformational behavior of the molecule with respect to the rotational position of the phenyl substituent, the semiempirical conformational analysis required additional assistance from thorough NMR investigations before the calculations of the CD spectra. Details will be published in a separate method-oriented paper.[12]

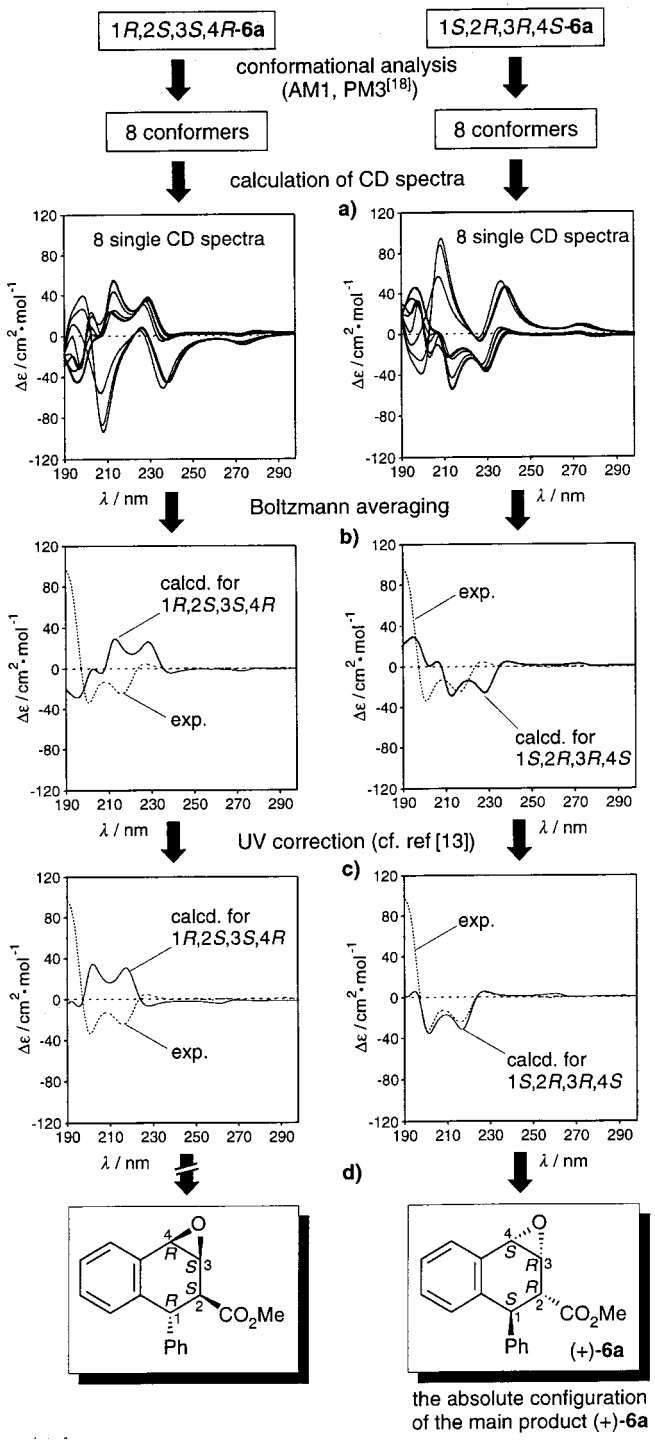


Figure 2. Route to the determination of the absolute configuration of the main product, epoxide (+)-**6a**.

The absolute configuration of the remaining dihydronaphthalene (−)-**5** was elucidated in the same way as for the main product **6a**. Again, eight minimum structures were found from conformational analysis. In accordance with the absolute configuration of the two products, the configuration of the remaining dihydronaphthalene should be 1*R*,2*R*. Conclusive evidence for this hypothesis was provided by comparison of the CD spectrum calculated for the 1*R*,2*R* and for the 1*S*,2*S* configurations with the experimental one. As shown in

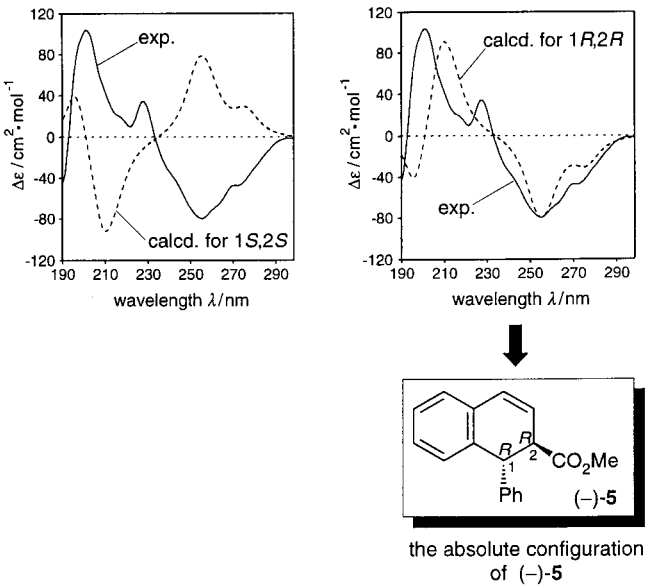


Figure 3. Elucidation of the absolute configuration of dihydronaphthalene (−)-**5**, by a route analogous to that in Figure 2.

Figure 3, the dihydronaphthalene (−)-**5** is unambiguously 1*R*,2*R*-configured, emphasizing again the reliability of quantum-chemical calculations of CD spectra as a tool for the elucidation of the absolute configuration of novel, natural or synthetic, chiral products.

Interestingly, all epoxidations exhibit a high degree of facial selectivity. Thus with the catalyst (*S*,*S*)-**7**, the predominant products (+)-**6a** and (−)-**6b** both have the same 3*R*,4*S* configuration in the epoxide ring. This result can be rationalized since the catalyst (*S*,*S*)-**7** prefers to attack chromenes and 1,2-dihydronaphthalenes at the designated face, independently of the substitution pattern; this is in accordance with literature examples for reactions of achiral substrates.[6] Furthermore, the face selectivities of these Jacobsen epoxidations more than compensate for the large steric demand of the phenyl group, which is responsible for the exclusive formation of one epoxide with MCPBA alone.[5a] Therefore, at higher conversions the catalyst (*S*,*S*)-**7** attacks the remaining dihydronaphthalene (−)-**5** *cis* to the phenyl group, resulting in the mismatched pair and the formation of epoxide (−)-**6b** as the by-product (Figure 4). Additionally, unfavorable polar interactions of the Jacobsen catalyst with the ester group have to be taken into account, which is

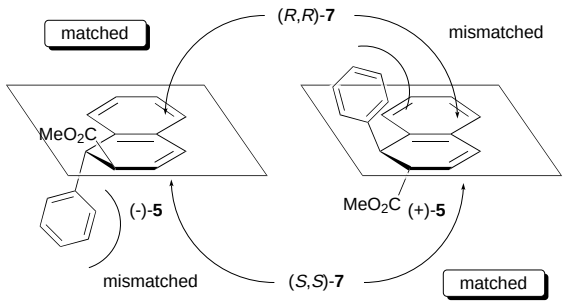


Figure 4. Mechanistic rationale for the face selectivities and the formation of two diastereomers from the dihydronaphthalene derivative *rac*-**5**.

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important for the mechanistic understanding of the Jacobsen–Katsuki epoxidation.[19]

In conclusion, kinetic resolution of the 1,2-dihydronaphthalenes *rac*-**5** by Jacobsen epoxidation proceeds smoothly and with good selectivity ($k_{rel} = 6.3-9.1$), a fact not hitherto realized. The proper choice of catalyst (*S*,*S*)-**7** or (*R*,*R*)-**7** allows the controlled synthesis of both epoxides (+)-**6a** and (−)-**6a** from the same starting material. For product analysis, complete separation of the enantiomers of the dihydronaphthalenes as well as the epoxides was achieved with HPLC on a chiral stationary phase. Furthermore, the absolute configuration of all the products was established unequivocally by comparison of experimental CD spectra with those obtained by quantum-chemical calculation. Finally, only one recrystallization was required to afford enantiomerically pure products, which can serve as valuable precursors for the synthesis of etoposide analogues.

Experimental Section

General methods: Solvents and commercially available chemicals were purified by standard procedures or used as purchased. TLC was performed on Polygram Sil G UV (40 × 80 mm), Macherey Nagel. Silica gel (63–200 μm, Woelm, Erlangen) was used for column chromatography. Melting points were measured on a Büchi SMP 20 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer. CD spectra were measured on a Dichrograph CD 6 spectrometer (Jobin Yvon) at room temperature in *n*-hexane. NMR spectra were recorded on either a Bruker AC 200 or a Bruker DRX-500 spectrometer at room temperature in $CDCl_3$. Chemical shifts are given on the δ scale; ^{1}H NMR spectra were referenced to internal TMS, and ^{13}C NMR spectra to the solvent $CDCl_3$ ($\delta CDCl_3 = 77.0$ ppm). Combustion analyses were carried out at the Microanalytical Division of the Institute of Organic Chemistry, University of Giessen (Germany).

HPLC analysis: The enantiomeric excesses of the dihydronaphthalene **5** and epoxide **6a** were determined by HPLC on a chiral stationary phase (Chiralcel OD-H; 0.5 mL min^{-1} hexane:isopropanol = 90:10, see Figure 1). A separation of the epoxide *rac*-**6b** by HPLC on a chiral phase was not possible.

Retention times: (+)-**5**: 12 min, (−)-**5**: 13 min, (+)-**6a**: 22 min, (−)-**6a**: 36 min.

Computational methods:

Conformational analyses: Conformational analyses were performed on Silicon Graphics IRIS 4D, INDIGO (R4000) workstations. For AM1[16] and PM3[17] calculations, the program package VAMP 6.1[20] was used, starting from geometries preoptimized by the TRIPOS[21] force field.

CD calculations: The wavefunctions for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained from CNDO/S-CI calculations[22] with a CI expansion including 576 singly occupied configurations and the ground state determinant. These calculations were carried out on LinuX workstations with the BDZDO/MCDSPD[23] program package. To obtain the theoretical, total CD spectrum, all single CD spectra were combined according to Boltzmann statistics using appropriate heats of formation. For better visualization, the rotational strengths were transformed into $\Delta\varepsilon$ values and superimposed with a Gaussian band shape function.

2-(4,4-Dimethyl-2-oxazolinyl)-naphthalene (**8**): To a solution of 2-naphthoic acid (**3**, 25.0 g, 0.145 mol) in dichloromethane (200 mL) was added dropwise a solution of thionyl chloride (25.9 g, 0.218 mol) in dichloromethane (160 mL) at 0 °C. After heating under reflux for 12 h, triethylamine (24.8 g, 0.245 mol) and a solution of 2-amino-2-methylpropanol (14.6 g, 0.164 mol) in dichloromethane (160 mL) were added dropwise at room temperature, and the whole stirred for 15 h. The precipitated hydrochloride was removed by filtration and the filtrate was concentrated under vacuum. The crude amidoalcohol was dissolved in a mixture of toluene (125 mL) and dichloromethane (180 mL) and a solution of thionylchloride (17.25 g, 0.145 mol) in dichloromethane (150 mL) was added dropwise at 0 °C. After heating under reflux for 1 h and stirring at room temperature for 12 h, the mixture was poured into cold 15 % aqueous sodium hydroxide, extracted with dichloromethane (4 × 100 mL), dried with anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was filtered through silica gel (hexane:ethyl acetate = 8:2) to afford the oxazoline **8** as pale-yellow crystals (26.1 g, 78 %; m.p. 47–49 °C, ref. [8] 46–48 °C); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.43$ (s, 6H, Me), 4.17 (s, 2H, CH_2), 7.47–7.92 (m, 5H, arom H), 8.03 (dd, $J = 8.5$, 1.7 Hz, 1H, arom H), 8.45 (s, 1H, arom H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 28.3$ (q, Me), 67.5 (s, $C(Me)_2$), 79.0 (t, CH_2O), 124.7, 126.3, 127.3, 127.6, 127.9, 128.5, 128.7 (7d, C arom), 124.8, 128.5, 132.5 (3s, C arom), 162.0 (s, C=N); IR (KBr): $\tilde{\nu} = 2970$ cm^{-1} (CH), 1714, 1638 (C=N).

2-(4,4-Dimethyl-2-oxazolinyl)-1-phenyl-1,4-dihydronaphthalene (**9**): Oxazoline **8** (450 mg, 2.0 mmol) was dissolved in anhydrous THF (5 mL) under an argon atmosphere at −78 °C. To this was added dropwise a solution of PhLi in THF (0.65 M, 6.2 mL, 4.0 mmol). The reaction mixture was stirred for 3 h at this temperature and then quenched with isopropanol (0.5 mL). After 6 h at room temperature, the mixture was poured into a saturated ammonium chloride solution (10 mL), extracted with dichloromethane (3 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. Column chromatography (hexane:ethyl acetate = 85:15) afforded the 1,4-dihydronaphthalene **9** as a colorless oil (440 mg 73 %, $R_f = 0.30$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.20$ (s, 3H, Me), 1.31 (s, 3H, Me), 3.63 (ddd, $J = 22.2$, 5.4, 2.5 Hz, 1H, 4-H), 3.70 (ddd, $J = 22.2$, 3.2, 2.8 Hz, 1H, 4′-H), 3.90 (d, $J = 10.4$ Hz, 1H, 5′-H), 3.91 (d, $J = 10.4$ Hz, 1H, 5″-H), 5.29 (dd, $J =$ 3.2, 2.5 Hz, 1H, 1-H), 6.97 (dd, $J = 5.4$, 2.8 Hz, 1H, 3-H), 7.11–7.29 (m, 9H, arom H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 28.0$ (s, CMe_2), 28.2 (q, Me), 30.4 (t, C-4), 45.9 (d, C-1), 78.4 (t, CH_2O), 115.6 (d, C-3), 126.0, 126.1, 126.2, 127.8, 128.0, 128.2, 128.3 (7d, C-5–C-8, C-Ph), 132.0, 135.9, 138.0, 144.5 (4s, C-2, C-9, C-10, C-Ph), 161.6 (s, C=N); IR (neat): $\tilde{\nu} = 2967$ cm^{-1} (CH), 1661, 1611 (C=N); $C_{21}H_{21}NO$ (303.4): calcd C 83.13, H 6.98, N 4.62; found C 83.04, H 7.13, N 4.65.

***trans*-1-Phenyl-1,2-dihydronaphthalene-2-carboxylic acid** (*rac*-**10**): Oxazoline **8** (22.53 g, 100 mmol) was dissolved in anhydrous THF (180 mL) under an argon atmosphere at −40 °C. To this was added dropwise a solution of PhLi in hexane:diethyl ether = 7:3 (2.06 M, 60 mL, 124 mmol). The reaction mixture was stirred for 3 h at this temperature. Then a mixture of TFA (30 mL, 389 mmol) and THF (20 mL) was added. After 10 min the reaction mixture was poured into a saturated ammonium chloride solution (200 mL) and extracted with diethyl ether (3 × 80 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and crystallized at 0 °C, directly yielding the desired ammonium salt (29.6 g, 68 %; m.p. 155–156 °C). Upon concentration of the mother liquor, a further crop of the product was obtained (7.4 g, 17 %). A solution of the ammonium salt (13.06 g, 30 mmol) in 3 N HCl (200 mL) was heated under reflux for 7.5 h under an argon atmosphere, cooled, and extracted with ethyl acetate (4 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and then concentrated under vacuum. Filtration through a short column of silica gel (hexane:ethyl acetate = 6:4) yielded the acid *rac*-**10** in the form of white crystals (7.35 g, 98 %; m.p. 121–122 °C); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 3.69 (ddd, $J = 7.6$, 4.5, 2.0 Hz, 1H, 2-H), 4.62 (d, $J = 7.6$ Hz, 1H, 1-H), 5.94 (dd, $J = 9.6$, 4.5 Hz, 1H, 3-H), 6.69 (dd, $J = 9.6$, 2.0 Hz, 1H, 4-H), 6.89 (d, $J = 7.2$ Hz, 1H, 8-H), 7.10–7.31 (m, 8H, arom H), 11.0 (br s, 1H, CO_2H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 45.2$ (d, C-1), 48.3 (d, C-2), 122.9, 126.6, 126.8, 127.1, 127.6, 128.1, 128.3, 128.5, 129.5 (9d, C-3–C-8, C-Ph), 132.3, 135.9, 142.8 (3s, C-9, C-10, C-Ph), 179.6 (s, CO_2H); IR (KBr): $\tilde{\nu} = 3100-2300$ cm^{-1} (COOH), 2880 (CH), 1707 (CO); $C_{17}H_{14}O_2$ (250.3): calcd C 81.58, H 5.64; found C 81.27, H 5.61.

Methyl *trans*-1-phenyl-1,2-dihydronaphthalene-2-carboxylate (*rac*-**5**): A solution of diazomethane in diethyl ether was added to a solution of the acid *rac*-**10** (2.5 g, 10 mmol) in dichloromethane (50 mL) at 0 °C until the yellow color persisted. After 12 h at 20 °C, the solution was concentrated and filtered through a short column of silica gel (hexane:ethyl acetate = 8:2) to yield the ester *rac*-**5** (2.62 g, 99 %); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 3.59 (s, 3H, OMe), 3.66 (ddd, $J = 8.5$, 4.3, 2.1 Hz, 1H, 2-H), 4.60 (d, $J =$ 8.5 Hz, 1H, 1-H), 5.90 (dd, $J = 9.6$, 4.3 Hz, 1H, 3-H), 6.62 (dd, $J = 9.6$, 2.1 Hz, 1H, 4-H), 6.84 (d, $J = 7.2$ Hz, 1H, 8-H), 7.05–7.31 (m, 8H, arom H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 45.8$ (d, C-1), 48.6 (d, C-2), 52.0 (q, OMe), 123.7, 126.5, 126.8, 127.0, 128.0, 128.3, 128.5, 128.6, 129.1 (9d, C-3–C-8, C-

Ph), 132.5, 136.2, 142.8 (3s, C-9, C-10, C-Ph), 173.5 (s, CO_2Me); IR (neat): $\tilde{\nu} = 3027\ cm^{-1}$ (CH), 2950 (CH), 1739 (CO); $C_{18}H_{16}O_2$ (264.3): calcd C 81.79, H 6.10; found C 81.47, H 5.97.

Epoxidation of the ester *rac*-5 with *m*-chloroperoxybenzoic acid: To a solution of ester *rac*-**5** (1.32 g, 5.0 mmol) in anhydrous dichloromethane (80 mL) was added 70% MCPBA (1.6 g, 6.1 mmol) at 0 °C. After 1.5 h the mixture was diluted with diethyl ether (200 mL) and extracted with saturated aqueous sodium sulfite (2 × 100 mL), saturated aqueous sodium hydrogencarbonate (2 × 100 mL), and brine (100 mL). The aqueous phases were extracted with diethyl ether (100 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Crystallization from diethyl ether yielded the epoxide *rac*-**6a** as white needles (1.32 g, 94%; m.p. 97–98 °C).

Typical procedure for asymmetric epoxidations in the presence of sodium hypochlorite: To a solution of 1,2-dihydronaphthalene *rac*-**5** (520 mg, 1.97 mmol), catalyst (*S*,*S*)-**7** (50 mg, 0.088 mmol, 0.04 equiv), and 4-PPNO (34 mg, 0.2 mmol, 0.1 equiv) in chlorobenzene (10 mL) was added 0.4 equiv of a sodium hypochlorite/sodium hydrogenphosphate solution (pH 11) at 0 °C. After 2 h the mixture was diluted with diethyl ether (50 mL) and immediately extracted with saturated aqueous sodium sulfite (2 × 20 mL) and brine (2 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered through a small pad of silica gel. Concentration under vacuum afforded 800 mg of the crude product, which was analyzed by NMR spectroscopy (conversion and product distribution). The product mixture was purified as described below for oxidations in the presence of *m*-chloroperoxybenzoic acid.

Typical procedure for asymmetric epoxidations in the presence of *m*-chloroperoxybenzoic acid: To a solution of 1,2-dihydronaphthalene *rac*-**2a** (860 mg, 3.25 mmol), catalyst (*S*,*S*)-**1a** (83 mg, 0.13 mmol, 0.04 equiv), and NMO (845 mg, 7.21 mmol, 2.2 equiv) in dichloromethane (35 mL) was added 70% MCPBA (720 mg, 2.9 mmol, 0.9 equiv) at −78 °C. After 1.5 h the mixture was diluted with diethyl ether (100 mL) and immediately extracted with saturated aqueous sodium sulfite (2 × 40 mL), saturated aqueous sodium hydrogencarbonate (2 × 40 mL), and brine (40 mL). The aqueous phases were extracted with diethyl ether (50 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. After filtration through a small pad of silica gel, concentration under vacuum afforded 1.06 g of the crude product, which was analyzed by NMR spectroscopy (conversion and product distribution). Column chromatography (hexane:ethyl acetate = 8:2) afforded the dihydronaphthalene (−)-**5** as a colorless oil (395 mg 46%; 57% *ee*), the epoxide (+)-**6a** as colorless needles (310 mg, 34%; 87% *ee*; m.p. 92–93 °C, and the epoxide (−)-**6b** as colorless needles (120 mg, 13%; m.p. 122–123 °C).

Recrystallization of the epoxide (+)-**6a** (87% *ee*) from hexane/diethyl ether afforded the enantiomerically pure epoxide (+)-**6a** as colorless needles (220 mg; m.p. 97–98 °C; $[\alpha]_D^{20} = +69.8$ ($c = 0.80$, $CHCl_3$). The corresponding enantiomerically pure epoxide (−)-**6a** was isolated as colorless needles (m.p. 97–98 °C; $[\alpha]_D^{20} = -70.2$ ($c = 1.04$, $CHCl_3$) (Table 1, entry 10) and the enantiomerically pure dihydronaphthalene (−)-**5** (Table 1, entry 8) as a colorless oil; $[\alpha]_D^{20} = -177.6$ ($c = 1.09$, $CHCl_3$).

Methyl (1*S*,2*R*,3*R*,4*S*)-1-phenyl-3,4-epoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (6a): ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.19$ (d $J = 12.0$ Hz, 1H, 2-H), 3.59 (s, 3H, OMe), 3.93 (d, $J = 4.2$ Hz, 1H, 3-H), 4.03 (d, $J = 4.2$ Hz, 1H, 4-H), 4.33 (d, $J = 12.0$ Hz, 1H, 1-H), 6.56 (dd, $J = 7.4$, 1.0 Hz, 1H, 8-H), 7.12–7.49 (m, 8H, arom H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 43.0 (d, C-1), 48.0 (d, C-2), 52.1 (q, OMe), 52.9 (d, C-4), 55.5 (d, C-3), 126.4, 127.2, 128.3, 128.6, 128.7, 129.5, 129.7 (7d, C-5, C-6, C-7, C-8, C-Ph), 131.1, 139.0, 140.1 (3s, C-9, C-10, C-Ph), 172.7 (s, CO_2Me); IR (KBr): $\tilde{\nu} =$ 2944 cm^{-1} (CH), 2958 (CH), 1733 (CO); $C_{18}H_{16}O_3$ (280.3): calcd C 77.13, H 5.75; found C 76.86, H 5.63.

Methyl (1*R*,2*S*,3*R*,4*S*)-1-phenyl-3,4-epoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (6b): ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.70$ (s, 3H, OMe), 3.74 (dd, $J = 2.5$, 1.3 Hz, 1H, 2-H), 3.96 (d, $J = 4.1$ Hz, 1H, 4-H), 3.96 (dd, $J = 4.1$, 2.5 Hz, 1H, 3-H), 4.73 (d, $J = 4.1$ Hz, 1H, 1-H), 7.11–7.49 (m, 9H, arom H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 46.3$, 45.7 (2d, C-1, C-2), 51.9 (d, C-4), 52.3 (q, OMe), 56.0 (d, C-3), 126.2, 127.1, 128.0, 128.6, 129.2, 129.9, 130.8 (7d, C-5, C-6, C-7, C-8, C-Ph), 132.4, 135.2, 145.4 (3s, C-9, C-10, C-Ph), 172.2 (s, CO_2Me); IR (neat): $\tilde{\nu} = 3024\ cm^{-1}$ (CH), 2952 (CH), 1736 (CO); $C_{18}H_{16}O_3$ (280.3): calcd C 77.13, H 5.75; found C 76.75, H 5.93.

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