Notes

Asymmetric Synthesis of the Dihydroisocoumarin Moiety of AI-77-B *via* Copper-Mediated Cross-Coupling and Sharpless Asymmetric Dihydroxylation

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AI-77s are a small family of antibiotics isolated from *Bacillus pumilus* which present as a common structural feature a dihydroisocoumarin moiety linked to acyl hydroxy amino acid chains which are different for the various members of the family.[1] The major compound of this group, named AI-77-B (**1**), has shown potent antiulcerogenic action against stress ulcer in rats without any anticholinergic, antihistaminergic or central suppressive effects.[2] Nowadays this compound presents a renewed interest in light of recent studies on antibiotic treatment for ulcer diseases.[3]

A number of total syntheses of **1** have been reported,[4] as well as some alternative procedures for the preparation of both the dihydroisocoumarin moiety **2**[5] and the hydroxy amino acidic portion.[6] Most of the approaches reported for the preparation of **2** involve as a key step the addition of *o*-toluic anions of esters or oxazolines to N-protected leucinal.[4] Nevertheless this approach presents some disadvantages, such as low yields, configurational lability of the required leucinal, and a low degree of diastereoselectivity in the toluate anion attack on the amino aldehyde, which usually gives a mixture of the two epimers at C-3. Recently two similar approaches to the synthesis of the dihydroisocoumarin **2** have been reported,[5] which present as key steps the reaction of 3-alkoxyphenyl Grignard reagents with chiral substrates,

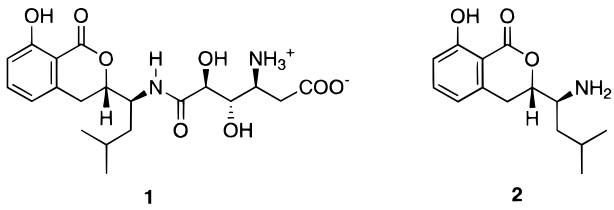

Figure 1.

respectively, a triflate[5a] and an epoxy alcohol,[5b] and the regioselective carboxylation of the aromatic ring.

In the course of studies on the synthesis and biological activity of dihydroisocoumarins,[7] we planned an alternative asymmetric route to **2**, based on the regioselective anionic allylation of *N*,*N*′-diethylbenzamides for the formation of the carbon skeleton,[8] and on Sharpless asymmetric dihydroxylation of the resulting olefin for the introduction of the chiral centers[9] (Scheme 1).

Results and Discussion

The regioselective *ortho*-alkylation of *N*,*N*′-diethyl-2-methoxybenzamide (**3**) was performed *via* a sequence of *ortho*-lithiation and copper-transmetalation of the amide. As a matter of fact, the widely used *ortho*-lithiated benzamides[10] cannot be used in cross-coupling reactions with aliphatic halides, whereas we showed that this reaction proceeds smoothly with the corresponding aryl cyanocuprate derivatives.[8] Amide **3** was lithiated by treatment with *s*-BuLi−TMEDA 1:1[11] and was then treated with a THF solution of CuCN·LiCl 1:1 complex. (*E*)-1-Bromo-5-methyl-2-hexene was added to the copper intermediate affording, in a one-pot sequence, the *o*-allylbenzamide **4** with a high yield. The stereoselective dihydroxylation of olefin **4**, performed in accordance with the Sharpless procedure,[12] produced simultaneously the two stereogenic centers present in the target molecule, with a very high degree of enantioselectivity. In detail, the allylbenzamide **4** was catalytically dihydroxylated in *t*-BuOH/H_2O solution, using $K_2OsO_2(OH)_4$ and 9-*O*-(9′-phenanthryl)-10,11-dihydroquinine (DHQ-PHN) as chiral ligand in the presence of $K_3Fe(CN)_6$ and K_2CO_3. The reaction afforded the amido-diol **5** of the desired (*S*,*S*) configuration, as confirmed by chemical correlation with the target compound **2** (*vide infra*), whose stereochemistry had already been assigned by X-ray analysis.[1] Besides, this stereochemical outcome was in agreement with the empirical rule reported by Sharpless.[12] It was not possible to determine the enantiomeric excess of **5** directly, because the hindered rotation of the benzamido

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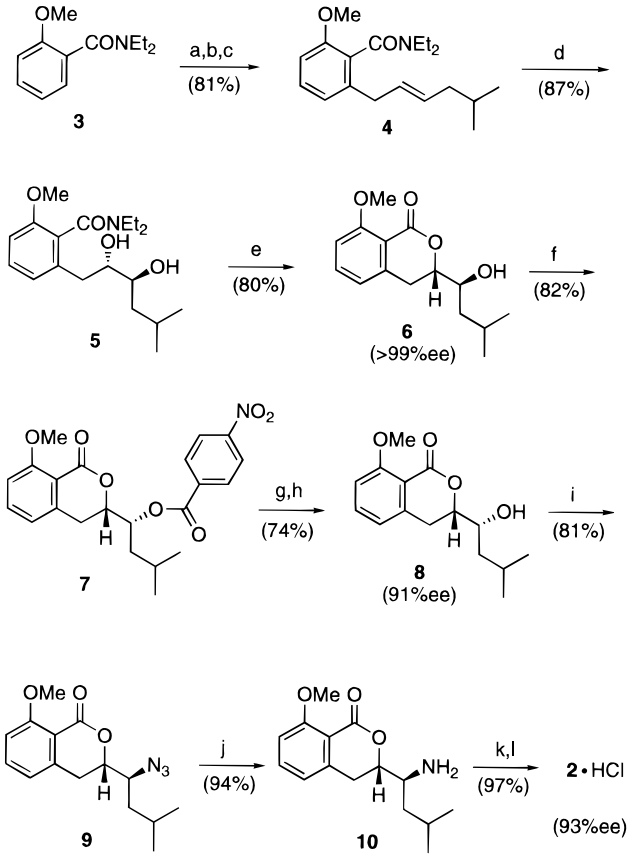
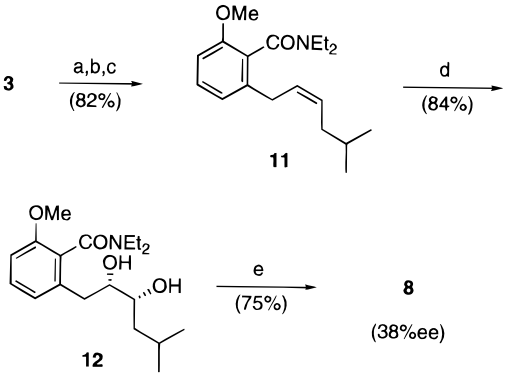
Scheme 1[a]



[a] Key: (a) *s*-BuLi/TMEDA, THF, −78 °C, 30 min; (b) CuCN·LiCl, −78 °C, 45 min; (c) (*E*)-1-bromo-5-methyl-2-hexene, −78 °C → rt, 4 h; (d) DHQ-PHN, $K_2OsO_2(OH)_4$, *t*-BuOH/H_2O (1:1), $K_3Fe(CN)_6$, K_2CO_3, 0 °C, overnight; (e) 50% NaOHaq/EtOH (1:1), reflux, 36 h; (f) *p*-nitrobenzoic acid, PPh_3, DEAD, toluene, rt, 2 h; (g) MeONa/MeOH, rt, 30 min; (h) Amberlite IR-120-H^+; (i) HN_3, PPh_3, DEAD, toluene, 0 °C → rt, overnight; (j) H_2, 5% Pd/C, MeOH, rt, 3 h; (k) BBr_3, CH_2Cl_2, −78 °C, 15 min; (l) 10% HCl in MeOH.

group[13] in this molecule generates an additional atropoisomeric chiral center, complicating both the HPLC and the NMR analysis. The diol **5** was cyclized in basic conditions[14] (EtOH/50% NaOH aq 1:1) to the dihydroisocoumarin **6**, which, after a single crystallization, showed an ee > 99% by HPLC analysis. The configuration of the chiral center bearing the OH-group had to be inverted, in order to obtain the target molecule **2**. The inversion was achieved by a Mitsunobu[15] esterification of the alcoholic functionality, using *p*-nitrobenzoic acid as the nucleophile,[16] to obtain the ester **7**, which was subsequently saponified with a diluted methanolic solution of sodium methoxide, to give the 1′-hydroxydihydroisocoumarin **8**, in 91% ee. It is worth nothing that hydrolysis of ester **7** in these conditions caused a minimal racemization of the substrate, whereas, carrying out the same reaction with sodium ethoxide in ethanol, we got **8** in only 40% ee.[17] The azido-derivative **9** was obtained in one step from **8** by a further Mitsunobu reaction with hydrazoic acid[16b] and the amine intermediate **10** by the catalytic hydrogenation of **9**. A sequence of demethylation with BBr_3 of the methyl aryl ether **10** and treatment with a methanolic solution of 10% HCl finally gave the target compound **2** as a hydrochloride, which showed an optical purity of 93%.

Scheme 2[a]



[a] Key: (a) *s*-BuLi/TMEDA, THF, −78 °C, 30 min; (b) CuCN·LiCl, −78 °C, 45 min; (c) (*Z*)-1-bromo-5-methyl-2-hexene, −78 °C → rt, 4 h; (d) DHQ-PHN, $K_2OsO_2(OH)_4$, *t*-BuOH/H_2O (1:1), $K_3Fe(CN)_6$, K_2CO_3, 0 °C, overnight; (e) 50% NaOHaq/EtOH (1:1), reflux, 36 h.

According to this synthetic procedure, a double inversion of configuration at C-1′ is required in order to obtain the right stereoisomer of **2**. This double step could have been skipped by starting the synthesis from the *cis* olefin **11**, as shown in Scheme 2.

We actually tried this path, which appeared to be more direct to the final product. The (*Z*) olefin **11**, prepared with a good yield from **3** and (*Z*)-1-bromo-5-methyl-2-hexene by the same procedure described for its (*E*) isomer **4**, was asymmetrically dihydroxylated as above. The diol **12** with the (*3S,1′R*) configuration was obtained with a good chemical yield, but with modest enantiomeric purity, as verified in the next cyclized product **8** (38% ee). This result is in agreement with the findings reported by other authors, in which *cis*-olefins, and especially the acyclic aliphatic ones, always give a low degree of enantioselectivity in the dihydroxylation reaction.[9] For this reason it was necessary to follow the longer, but more enantiospecific, approach reported in Scheme 1.

The procedure described in this paper for the synthesis of the dihydroisocoumarin portion common to AI-77 antibiotics appears to be very efficient and stereoselective. This approach is also potentially versatile for the preparation of different regio- and stereoisomers of **2**. As a matter of fact the regioselectivity of benzamide alkylation is independent from the position of the methoxy group on the ring, allowing the synthesis of different regioisomers of **2**, while the choice of the appropriate dihydroxylation catalyst combined with selective epimerization of the chiral centers can lead to four possible stereoisomers of the molecule. This potential of the approach reported can be very interesting in order to

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conduct systematic studies on the structure-activity relationship of AI-77s and related compounds.

Experimental Section

General Procedures. Melting points are uncorrected. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ unless otherwise stated. Analytical TLC was performed on 0.2 mm silica gel plate Merck 60 F-254 and flash chromatography[18] was carried out with silica gel Merck 60 (230−400 mesh). Enantiomeric purity of products was determined by HPLC using chiral column Daicel Chiralpak (+) AD. Metalations were performed using syringe-septum cap techniques under argon atmosphere. *sec*-Butyllithium (Aldrich) was a 1.3 M solution in cyclohexane−heptane, whose exact titer was determined by titration using 2,5-dimethoxybenzyl alcohol.[19] TMEDA (Aldrich) was distilled from CaH_2 and stored over 4 Å molecular sieves. THF and toluene were distilled over sodium immediately before use, and CH_2Cl_2 was distilled and stored over $CaCl_2$. The solution of anhydrous HN_3 in benzene was prepared according to a literature procedure.[20] (*E*)- and (*Z*)-1-bromo-5-methyl-2-hexene were prepared, respectively, from (*E*)-[21] and (*Z*)-5-methyl-2-hexen-1-ol,[22] and *N*,*N*′-diethyl-2-methoxybenzamide (**3**) from *o*-anisic acid.

***(E)*-2-(5′-Methyl-2′-hexenyl)-6-methoxy-*N*,*N*′-diethylbenzamide (4).** To a solution of *s*-BuLi (1.3 M, 10 mL, 13 mmol) and TMEDA (1.96 mL, 13 mmol) in dry THF (50 mL) was slowly added, at −78 °C, a solution of *N*,*N*′-diethyl-2-methoxybenzamide (**3**) (2.45 g, 11.8 mmol) in THF (15 mL), and the mixture was stirred for 30 min. Then was added a solution of CuCN (1.164 g, 13 mmol) and LiCl (551 mg, 13 mmol) in THF (20 mL). After 45 min of stirring was added a solution of (*E*)-1-bromo-5-methyl-2-hexene (2.30 g, 13 mmol) in THF (25 mL). The mixture was then slowly warmed to room temperature while stirring and after 4 h quenched with water and diluted with Et_2O. The organic layer was repeatedly treated with saturated aqueous NH_4Cl and brine and dried over Na_2SO_4. Evaporation of solvent afforded an oily residue which, after flash-chromatography (petroleum ether/EtOAc 2:1), yielded 2.89 g of olefin **4** (81% yield) as a viscous oil: ^{1}H NMR δ 0.87 (d, J = 6.6 Hz, 6H), 1.02 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.5−1.7 (m, 1H), 1.8−1.9 (m, 2H), 3.0−3.5 (m, 5H), 3.7−3.8 (m, 1H), 3.79 (s, 3H), 5.4−5.5 (m, 2H), 6.73 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H); ^{13}C NMR δ 12.72, 13.64, 22.23, 28.34, 35.70, 38.34, 41.84, 42.57, 55.38, 108.21, 121.47, 128.81, 129.05, 129.14, 131.11, 138.81, 155.25, 168.03; MS (EI) m/z 303 (M^+, 78), 260 (90), 231 (33), 174 (100), 91 (26). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.73; H, 7.82; N, 4.69.

2-[(2′S,3′*S*)-2′,3′-Dihydroxy-5′-methylhexyl]-6-methoxy-*N*,*N*′-diethylbenzamide (5). A mixture of olefin **4** (2.43 g, 8 mmol), DHQ-PHN[23] (330 mg, 0.66 mmol), $K_2OsO_2(OH)_4$ (22 mg, 0.06 mmol), $K_3Fe(CN)_6$ (7.90 g, 24 mmol), and K_2CO_3 (3.32 g, 24 mmol) in H_2O/*t*-BuOH 1:1 (100 mL) was stirred overnight at 0 °C and then warmed at room temperature, and $NaHSO_3$ (11.4 g) was added. The mixture was stirred 45 min at room temperature and then diluted with EtOAc and water. The aqueous phase was extracted with EtOAc, and the organic phases were washed with 1 M H_2SO_4, 10% aqueous $NaHCO_3$, and brine and dried over Na_2SO_4. The residue was collected after evaporation of solvent and was purified by flash-chromatography (petroleum ether/EtOAc 1:1), affording 2.34 g (87% yield) of diol **5**: MS (EI) m/z: 337 (M^+, 26), 305 (39), 262 (43), 175 (100), 149 (66). Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.51; H, 9.34; N, 4.06.

(3*S*)-3-[(1′*S*)-1′-Hydroxy-3′-methylbutyl]-8-methoxy-3,4-dihydroisocoumarin (6). Diol **5** (2.0 g, 5.9 mmol) was treated with a mixture of 50% aqueous NaOH (60 mL) and EtOH (60 mL) and the mixture heated under reflux for 36 h. Then EtOH was distilled off and the residue neutralized with concd HCl at 0 °C. The aqueous phase was extracted three times with EtOAc, and the collected organic solutions were washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. After evaporation of solvent, the solid residue was purified by flash-chromatography (petroleum ether/EtOAc 1:2) yielding 1.25 g (80% yield) of the dihydroisocoumarin **6**. Upon recrystallization from Et_2O was collected 968 mg of **6** as colorless needles, which showed ee > 99%: mp 98−99 °C; $[\alpha]^{25}_D$ = −145.7° (*c* 0.18, CH_3OH); UV (CH_3OH, 0.45 mg mL^{-1}) λ_{max} (nm) (ϵ_{max}, M^{-1} cm^{-1}) 208 (23000), 245 (8000), 309 (4000); CD (CH_3OH, 0.45 mg mL^{-1}) λ_{max} (nm) ($\Delta\epsilon_{max}$, M^{-1} cm^{-1}): 200 (−8.0), 226 (0), 237 (+1.6), 245 (0), 257 (−3.6), 284 (−1.1), 304 (−1.6), 331 (0); ^{1}H NMR δ 0.95 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 1.2−1.4 (m, 2H), 1.8−2.0 (m, 1H), 2.23 (d, J = 7.0 Hz, 1H), 2.78 (dd, J = 16.0, 2.6 Hz, 1H), 3.18 (dd, J = 16.0, 12.4 Hz, 1H), 3.7−3.9 (m, 1H), 3.96 (s, 3H), 4.26 (ddd, J = 12.4, 4.5, 2.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H); ^{13}C NMR δ 21.69, 23.49, 24.24, 31.02, 41.61, 56.15, 70.76, 80.79, 110.84, 113.50, 119.40, 134.66, 141.86, 161.16; MS (EI) m/z 264 (M^+,-10), 177 (100), 149 (81), 91 (16). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.10; H, 7.57.

(3*S*)-3-[(1′*R*)-1′-*p*-Nitrobenzoyl-3′-methylbutyl]-8-methoxy-3,4-dihydroisocoumarin (7). To a solution of dihydroisocoumarin **6** (450 mg, 1.70 mmol) in dry toluene (20 mL) were added PPh_3 (1.077 g, 4.08 mmol) and *p*-nitrobenzoic acid (611 mg, 3.65 mmol). To the resulting heterogeneous mixture was dropwise added DEAD (0.65 mL, 4.1 mmol), and the yellow solution was stirred for 2 h at room temperature. The solvent was evaporated, and the recovered residue was purified by flash-chromatography (petroleum ether/EtOAc 1:1) yielding 577 mg (82% yield) of the dihydroisocoumarin **7** as a slightly yellow solid: mp = 103−104 °C; $[\alpha]^{25}_D$ = −87.6° (*c* 0.26, CH_3OH); UV (CH_3OH, 0.47 mg mL^{-1}) λ_{max} (nm) (ϵ_{max}, M^{-1} cm^{-1}) 205 (34000), 247 (16000), 279 (7800), 297 (5800); CD (CH_3OH, 0.47 mg mL^{-1}) λ_{max} (nm) ($\Delta\epsilon_{max}$, M^{-1} cm^{-1}) 200 (−9.7), 222 (0), 235 (+0.82), 241 (0), 255 (−2.7), 275 (−1.0), 303 (−3.1), 338 (0); ^{1}H NMR δ 0.98 (d, J = 6.2 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H), 1.6−1.8 (m, 2H), 1.9−2.1 (m, 2H), 2.90 (dd, J = 16.0, 2.8 Hz, 1H), 3.14 (dd, J = 16.0, 11.9 Hz, 1H), 3.94 (s, 3H), 4.58 (ddd, J = 11.9, 4.2, 2.8 Hz, 1H), 5.4−5.6 (m, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 7.47 (dd, J = 8.5, 7.6 Hz, 1H), 8.2−8.3 (m, 4H); ^{13}C NMR δ 21.93, 23.33, 24.59, 30.42, 38.56, 56.20, 73.92, 78.09, 111.17, 113.52, 119.92, 123.60, 130.90, 134.76, 135.21, 140.96, 150.73, 161.33, 164.11; MS (EI) m/z 413 (M^+, 21), 246 (7), 203 (20), 177 (100), 149 (97), 91 (56). Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.61; N, 3.39. Found: C, 63.88; H, 5.60; N 3.35.

(3*S*)-3-[(1′*R*)-1′-Hydroxy-3′-methylbutyl]-8-methoxy-3,4-dihydroisocoumarin (8). The nitrobenzoyl ester **7** (530 mg, 1.28 mmol) was dissolved in dry methanol (35 mL) and treated with a solution of sodium methoxide (8.35 mL, 1.3 M in methanol, 11 mmol). The mixture was stirred 30 min at room temperature and then neutralized with Amberlite IR-120-H$^+$ and filtered, the solvent evaporated. The collected residue was purified by flash-chromatography (petroleum ether/EtOAc 1:1) yielding 250 mg (74% yield) of the dihydroisocoumarin **8** as colorless solid, which showed 91% ee: mp 99−101 °C; $[\alpha]^{25}_D$= −148.8° (*c* 0.13, CH_3OH) {lit.[5a] $[\alpha]^{21}_D$ = −155.6° (*c* 0.64, $CHCl_3$)}; UV (CH_3OH, 0.46 mg mL^{-1}) λ_{max} (nm) (ϵ_{max}, M^{-1} cm^{-1}) 208 (23000), 243 (8000), 311 (4000); CD (CH_3OH, 0.46 mg mL^{-1}) λ_{max} (nm) ($\Delta\epsilon_{max}$, M^{-1} cm^{-1}) 200 (−6.2), 227 (0), 239 (+1.7), 247 (0), 259 (−3.2), 283 (−0.86), 304 (−1.5), 332 (0); ^{1}H NMR δ 0.94 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 1.2−1.3 (m, 1H), 1.4−1.6 (m, 1H), 1.8−1.9 (m, 1H), 2.35 (d, J = 3.7 Hz, 1H), 2.78 (dd, J = 16.4, 2.6 Hz, 1H), 3.20 (dd, J = 16.4, 12.6 Hz, 1H), 3.95 (s, 3H), 4.0−4.1 (m, 1H), 4.31 (ddd, J = 12.6, 3.3, 2.4 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 7.47 (dd, J = 8.5, 7.6 Hz, 1H); ^{13}C NMR δ 21.63, 23.49, 24.24, 31.02, 41.61, 56.15, 70.76, 80.79, 110.84, 113.50, 119.40, 134.66, 141.86, 161.16; MS (EI) m/z 264 (M^+, 11), 177 (100), 149 (81). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.08; H, 7.72.

(3*S*)-3-[(1′*S*)-1′-Azido-3′-methylbutyl]-8-methoxy-3,4-dihydroisocoumarin (9). To a mixture of **8** (230 mg, 0.87 mmol) and PPh_3 (457 mg, 1.74 mmol) in dry toluene (20 mL) was

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(23) The use of $(DHQ)_2$-PHAL, a more recent chiral ligand in the AD reaction, did not improve the enantioselectivity.

dropwise added DEAD (0.27 mL, 1.7 mmol) at 0 °C, followed by a solution of HN_3 (1.32 mL, 1.13 M in benzene, 1.5 mmol). The mixture was stirred overnight at room temperature and then diluted with *n*-hexane. The formed precipitate was filtered off and the solvent evaporated. The residue was purified by flash-chromatography (petroleum ether/EtOAc 1:1) yielding 205 mg (81% yield) of the azide **9** as colorless glass: $[\alpha]^{25}_D = -202°$ (*c* 0.11, CH_3OH) {lit.[5a] $[\alpha]^{22}_D = -169.6°$ (*c* 1.12, $CHCl_3$)}; UV (CH_3OH, 0.51 mg mL^{-1}) λ_{max} (nm) (ϵ_{max}, M^{-1} cm^{-1}) 205 (23000), 244 (9600), 298 (3700); CD (CH_3OH, 0.51 mg mL^{-1}) λ_{max} (nm) ($\Delta\epsilon_{max}$, M^{-1} cm^{-1}) 200 (−14.6), 226 (0), 237 (+1.5), 243 (0), 256 (−5.0), 284 (−1.6), 302 (−2.5), 333 (0); ^{1}H NMR δ 0.95 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H), 1.2−1.3 (m, 1H), 1.5−1.6 (m, 1H), 1.8−2.0 (m, 1H), 2.76 (dd, J = 16.0, 2.6 Hz, 1H), 3.17 (dd, J = 16.0, 12.4 Hz, 1H), 3.4−3.5 (m, 1H), 3.92 (s, 3H), 4.39 (ddd, J = 12.4, 4.1, 2.6 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 7.45 (dd, J = 8.6, 7.5 Hz, 1H); ^{13}C NMR δ 21.56, 23.07, 24.79, 31.15, 38.21, 56.12, 61.33, 78.84, 110.95, 113.34, 119.25, 134.66, 141.27, 161.16; MS (EI) *m*/*z* 289 (M^+, 35), 261 (70), 177 (100), 149 (99), 91 (81). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.22; H, 6.65; N, 14.63.

(3*S*)-3-[(1′*S*)-1′-Amino-3′-methylbutyl]-8-methoxy-3,4-dihydroisocoumarin (10). A mixture of **9** (130 mg, 0.45 mmol) and 5% Pd/C (63 mg, 0.03 mmol) in methanol was stirred 3 h in a hydrogen atmosphere. The mixture was then filtered over Celite, the residue washed with methanol, and the filtrate evaporated, yielding 112 mg of **10** (94% yield) as a viscous oil, which was used without further purification: $[\alpha]^{25}_D = -50°$ (*c* 0.17, CH_3OH); UV (CH_3OH, 0.43 mg mL^{-1}) λ_{max} (nm) (ϵ_{max}, M^{-1} cm^{-1}) 201 (23000), 240 (11000), 295 (3600); CD (CH_3OH, 0.43 mg mL^{-1}) λ_{max} (nm) ($\Delta\epsilon_{max}$, M^{-1} cm^{-1}) 200 (+1.2), 204 (0), 211 (−2.1), 220 (0), 226 (+0.44), 233 (+0.13), 242 (+0.76), 251 (0), 274 (−1.9), 279 (−0.91), 290 (−1.2), 325 (0); ^{1}H NMR δ 0.80 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 1.2−1.8 (m, 3H), 2.71 (dd, J = 13.3, 9.6 Hz, 1H), 3.07 (dd, J = 13.2, 6.9 Hz, 1H), 3.1−3.2 (m, 1H), 3.87 (s, 3H), 3.9−4.0 (m, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H); ^{13}C NMR δ 22.24, 22.92, 24.57, 38.32, 40.87, 53.31, 56.09, 75.29, 110.93, 121.00, 123.21, 131.37, 136.80, 157.97, 169.32; MS (EI) *m*/*z* 263 (M^+, 58), 220 (100), 177 (68), 149 (46). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.28; H, 8.20; N, 5.41.

(3*S*)-3-[(1′*S*)-1′-Amino-3′-methylbutyl]-8-hydroxy-3,4-dihydroisocoumarin Hydrochloride (2·HCl). The dihydroisocoumarin **10** (95 mg, 0.36 mmol) was dissolved in dry CH_2Cl_2 (35 mL), and a solution of BBr_3 (0.14 mL, 1.5 mmol) in CH_2Cl_2 (5 mL) was dropwise added at −78 °C. The mixture was stirred at that temperature for 15 min and then quenched with H_2O (5 mL), diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine and dried over Na_2SO_4. After evaporation of solvent, the recovered residue was dissolved again in CH_2Cl_2 and treated with 10% methanolic HCl. The mixture was then concentrated recovering 101 mg of **2**·HCl (97% yield) as a slightly brown solid, whose spectroscopic and analytical data were in agreement with those reported:[4c,5b] mp = 204−205 °C; $[\alpha]^{25}_D = -44.1°$ (*c* 0.13, MeOH) {lit.[4c]: $[\alpha]^{22}_D = -47.42°$ (*c* 0.11, MeOH)}; ion-spray MS m/z 250 ($M - Cl^-$); ion-spray MS/MS: m/z 250 ($M - Cl^-$, 84), 232 (33), 176 (97), 162 (100), 133 (87). Anal. Calcd for $C_{14}H_{20}NO_3Cl$: C, 58.84; H, 7.05; N, 4.90; Cl, 12.41. Found: C, 59.03; H, 7.12; N, 4.98; Cl, 12.07.

***(Z)*-2-(5′-Methyl-2′-hexenyl)-6-methoxy-*N*,*N*′-diethylbenzamide (11).** To a solution of *s*-BuLi (1.3 M, 8.2 mL, 11 mmol) and TMEDA (1.6 mL, 11 mmol) in dry THF (60mL) was slowly added at −78 °C a solution of *N*,*N*′-diethyl-2-methoxybenzamide (**3**) (2.0 g, 9.6 mmol) in THF (20 mL). The resulting mixture was stirred for 30 min and then was added a solution of CuCN (0.96 g, 11 mmol) and LiCl (454 mg, 11 mmol) in THF (20 mL). After 45 min of stirring, a solution of (*Z*)-1-bromo-5-methyl-2-hexene (1.9 g, 11 mmol) in THF (15 mL) was added. The mixture was then slowly warmed to rt while stirring and, after 4 h, was quenched with water and diluted with Et_2O. The organic layer was repeatedly washed with saturated aqueous NH_4Cl solution and brine and dried over anhyd Na_2SO_4. Evaporation of solvent afforded an oily residue which, after flash chromatography (*n*-hexane/EtOAc 1:1), yielded 2.43 g of olefin **11** (82% yield) as a colorless oil: ^{1}H NMR δ 0.89 (d, J = 6.6 Hz, 6H), 1.02 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.5−1.7 (m, 2H), 1.9−2.0 (m, 1H), 3.0−3.2 (m, 2H), 3.2−3.5 (m, 3H), 3.7−3.8 (m, 1H), 3.77 (s, 3H), 5.5−5.6 (m, 2H), 6.72 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 7.21 (t, J = 8.1 Hz, 1H); ^{13}C-NMR δ 12.71, 13.63, 22.32, 28.56, 30.18, 36.28, 38.39, 42.53, 55.39, 108.26, 121.19, 127.70, 129.12, 130.03, 138.85, 155.22, 168.02; MS (EI) *m*/*z* 303 (M^+, 58), 260 (64), 232 (100), 175 (76), 161 (79). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found C, 76.65; H, 7.92; N, 4.66.

2-[(2′*S*,3′*R*)-2′,3′-Dihydroxy-5′-methylhexyl]-6-methoxy-*N*,*N*′-diethylbenzamide (12). A mixture of olefin **11** (1.00 g, 3.30 mmol), DHQ-PHN (138 mg, 0.275 mmol), $K_2OsO_2(OH)_4$ (9.1 mg, 0.025 mmol), $K_3Fe(CN)_6$ (3.26 g, 9.90 mmol), and K_2CO_3 (1.37 g, 9.90 mmol) in *t*-BuOH/H_2O 1:1 (50 mL) was stirred overnight at 0 °C, and then $NaHSO_3$ (5.5 g) was added. The mixture was warmed at rt and stirred for 1 h and then diluted with EtOAc and water. The aqueous phase was repeatedly extracted with EtOAc. The organic phases were washed with 1 M H_2SO_4, 10% aqueous $NaHCO_3$, and brine and dried over Na_2SO_4. The solid residue, collected after evaporation of solvent, was purified by flash-chromatography (petroleum ether/EtOAc 1:1) affording 0.93 g (84% yield) of diol **12**. MS (EI) *m*/*z* 337 (M^+, 19), 250 (41), 221 (35), 206 (56), 175 (100), 149 (66). Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.47; H, 9.33; N, 4.08.

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