

Synthesis of Optically Active Monoacid Side-Chains of *Cephalotaxus* Alkaloids

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The general preparation of enantiopure monoacid side-chains of several esters of cephalotaxine is described. The strategy, similar to Weinreb's approach to the synthesis of deoxyharringtonine, used as key intermediate the chiral nonracemic epoxide **11a** prepared from the commercially available monomethyl itaconate (**8**). The key step of the strategy was the ring-opening of the epoxide **11a** by using different organo-

cuprate nucleophiles. Hydrogenolysis as the final step gave the monoacid side-chains of the corresponding esters of cephalotaxine in moderate to good overall yields from epoxide **11a**.

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Introduction

Several alkaloids isolated from the genus *Cephalotaxus* (evergreen conifers and shrubs) have been shown to exhibit interesting antileukemic activities.^[1] Among them harringtonine (**1**), deoxyharringtonine (**2**), homodeoxyharringtonine (**3**), neoharringtonine (**4**), anhydroharringtonine (**5**), and homoharringtonine (**6**) have been studied extensively.^[2] Homoharringtonine is the most potent in this family of antitumor alkaloids. Indeed, it is currently in phase II–III of clinical trials in the United States for the treatment of chronic myeloid leukaemia.^[3] The limited availability of these alkaloids has led to the development of a number of strategies for their synthesis. The products are all esters of cephalotaxine (**7**), the most abundant alkaloid extracted from *Cephalotaxus*, and could be used as the starting material for their hemisynthesis (Figure 1). Cephalotaxine itself does not exhibit any interesting antitumor activity.^[4]

It thus appears that the bioactivity of the natural esters is closely related to the acid side-chains. Moreover, these types of α -alkyl malates are an important part of many other bioactive compounds^[5] and, as for the cephalotaxine esters, their biological activity is linked to the nature of the side-chains. Several methods have been reported for the synthesis of the individual side-chains.^[6] One of the challenges in the synthesis of the side-chains of esters of cephalotaxine is to obtain a general and enantioselective procedure by using the same intermediate for all chains. Up to now the only general strategy had been reported recently by Tietze and co-workers,^[7] who prepared the side-chains of **1–6** from a unique intermediate. Their approach was

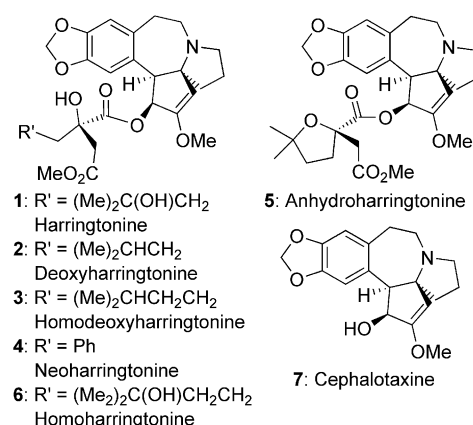
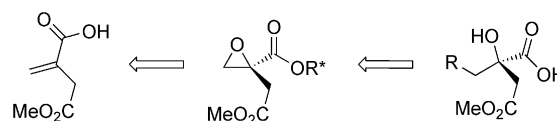


Figure 1. Structures of some natural esters of *Cephalotaxus*.

based upon Seebach's procedure for the alkylation of D-malic acid with self-regeneration of the stereogenic centers.

Herein we wish to report a general procedure for the preparation of some enantiomerically enriched monoacid side-chains based upon the approach of Weinreb and co-workers developed for the racemic synthesis of the deoxyharringtonine side-chain.^[6c] Our strategy (Scheme 1) uses a functionalized chiral nonracemic epoxide as the key intermediate of the synthesis, which was prepared in good yield and optical purity. A general epoxide ring-opening procedure using organocuprates as nucleophiles led to various side-chains.



Scheme 1. Retrosynthetic scheme.

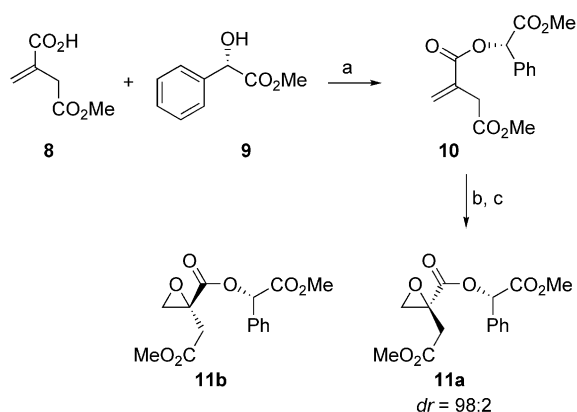
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Results and Discussion

One of the main difficulties in our approach is the control of the asymmetric carbon atom in the side-chains. We envisaged introducing asymmetry through a chiral nonracemic functionalized epoxide, the quaternary center of which had the desired absolute configuration. The side-chains would then be obtained by epoxide ring-opening with appropriate nucleophiles.

The two main criteria we defined for this key chiral epoxide intermediate were the following: (1) Easy preparation on a large scale (laboratory scale) and (2) orthogonal protection of the two ester groups, which allows the preparation of the monoacid derivative before or after the epoxide ring-opening.

These criteria dictated the use of epoxide **11** (Scheme 2). It appeared to be easily available from methyl itaconate (**8**), which could be esterified with methyl mandelate (**9**) before epoxidation of the double bond. The presence of the mandelate ester as a chiral appendage would permit the introduction of chirality and easy deprotection under hydrogenolysis conditions.



Scheme 2. Synthesis of epoxide **11a**. Reagents and conditions: (a) DCC, DMAP, DCM, room temperature, 5 h (96%); (b) *m*-CPBA (>95% purity), radical inhibitor, DCE, reflux, 16 h (72%); (c) flash chromatography.

Esterification of commercially available monomethyl itaconate (**8**) with enantiopure methyl mandelate (**9**) in the presence of DCC and DMAP furnished the diester **10** in

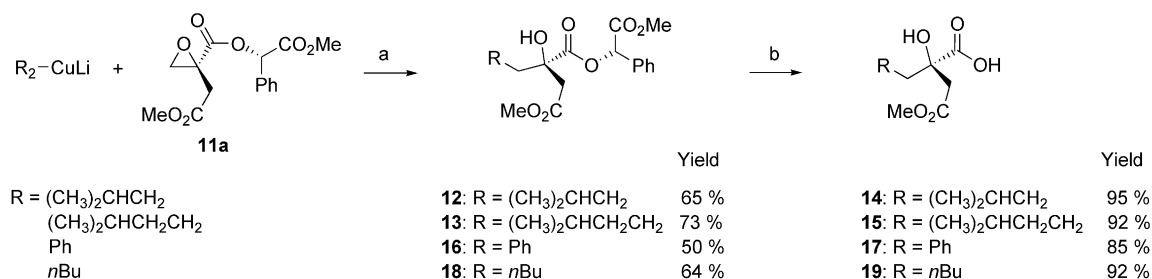
96% yield. The alkene diester **10** was epoxidized by using 2 equiv. of enriched *m*-CPBA^[8] (>95% purity) and 2,4,6-tri-*tert*-butylphenol as radical inhibitor. This reaction was also carried out with commercially available *m*-CPBA (ca. 70% purity) and gave a similar yield, but in this case the peracid had to be used in large excess (6 equiv.). The epoxide was obtained in 72% optimized yield as a 1:1 mixture of two diastereomers. No chiral induction was observed in this epoxidation; the asymmetric carbon atom of the mandelic ester was probably too distant to induce any facial stereoselectivity during the reaction. Fortunately, the two diastereomers were separated by flash chromatography, and the desired compound **11a** with the (*S,S*) configuration was isolated in 96% *de* (Scheme 2).

Having secured the absolute configuration of the quaternary carbon atom in **11a**, various side-chains could be introduced through chemoselective ring-opening of the epoxide with appropriate nucleophiles. Organocuprate reagents are often used for this type of reaction.^[9] First, we tried to apply this strategy to the synthesis of the deoxy- and homodeoxyharringtonine side-chains. The lower-order Gilman organocuprates were prepared as reported in the literature from the corresponding lithium derivatives: Isobutyl- or isopentyllithium (prepared from the corresponding bromide reagents in diethyl ether at 0 °C) (2 equiv.) and CuI in diethyl ether as solvent.^[10]

Epoxide **11a** readily reacted with isobutyl- and isopentylcuprates in diethyl ether at –78 °C to give the deoxy- and homodeoxyharringtonine side-chain diesters **12** and **13** in 65 and 73% yields, respectively (Scheme 3).

The monoacid side-chains were then prepared by selective cleavage of the mandelic ester by hydrogenolysis using palladium on charcoal as catalyst in ethyl acetate and under hydrogen at room temperature and atmospheric pressure.^[11] The monoacid side-chains of deoxy- and homodeoxyharringtonines **14** and **15** were obtained in 95 and 92% yields, respectively (62 and 67% overall yields from epoxide **11a**).

According to the same sequence starting from the reaction of phenylcuprate with epoxide **11a** and then hydrogenolysis of the mandelic ester, the monoacid side-chain **17** of neoharringtonine was prepared in 43% overall yield. However, and surprisingly, hydrogenolysis of the mandelic ester under the conditions described above did not afford

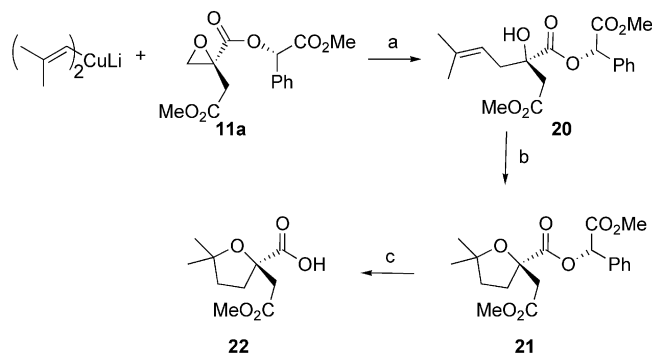


Scheme 3. Synthesis of monoacid side-chains of deoxyharringtonine, homodeoxyharringtonine, neoharringtonine, and a non-natural side-chain from epoxide **11a**. Reagents and conditions: (a) Et₂O, –78 °C to –60 °C, 2 h; (b) H₂, Pd/C, AcOEt, room temperature, 5 h or Pd(OH)₂, AcOEt, room temperature, 5 bar, 5 h.

the monoacid product, and the starting material was recovered unchanged. After several trials, hydrogenolysis was achieved by using palladium hydroxide as the catalyst in ethyl acetate under 5 bar of hydrogen for 5 h. The monoacid side-chain of the neoharringtonine **17** was obtained in a good 85% yield.

We eventually applied this strategy to the synthesis of a non-natural monoacid side-chain, the structure of which is similar to the homodeoxyharringtonine. The organocuprate was prepared from commercially available *n*-butyllithium. The monoacid side-chain **19** was synthesized in 59% overall yield from the key intermediate epoxide **11a** by using the same procedure (Scheme 3). Thus, we have shown that the aliphatic side-chains can be synthesized in good yields by using this simple and efficient procedure.

The addition of 2-methylpropen-1-ylcuprate to **11a** allowed the preparation of the side-chain of anhydroharringtonine **5**. The tertiary alcohol intermediate **20** was obtained in a moderate 55% yield by ring-opening of **11a** with the copper reagent. The furan ring was formed by hydroxymercuration followed by spontaneous cyclization^[12] to give **21** in 76% yield (Scheme 4).

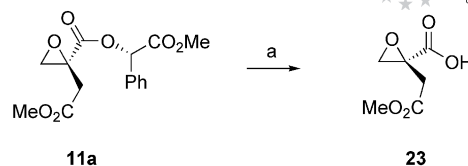


Scheme 4. Synthesis of anhydroharringtonine monoacid side-chain from epoxide **11a**. Reagents and conditions: (a) Et_2O , -78 to -60 °C, 2 h (55%); (b) $\text{Hg}(\text{OAc})_2$, NaBH_4 , $\text{THF}/\text{H}_2\text{O}$, 0 °C to room temperature, 2.5 h (76%); (c) H_2 , Pd/C , AcOEt , room temperature, 5 h (90%).

Finally, the target acid **22** was obtained in 90% yield after hydrogenolysis under the previously described conditions. This side-chain corresponding to anhydroharringtonine was synthesized in three steps from epoxide **11a** in 42% overall yield. The harringtonine monoacid side-chain could probably be synthesized by this method with prior protection of the free hydroxy group followed by hydroxymercuration of the double bond.

We also showed that it was possible to hydrogenolyze the epoxide **11a** to generate the corresponding monoacid. The hydrogenolysis was carried out in THF by using a catalytic amount of palladium hydroxide at room temperature and atmospheric pressure for 2 h. The monoacid epoxide **23** was obtained in 70% yield (Scheme 5).

It has been reported that direct esterification of a side-chain with cephalotaxine was not possible because of steric hindrance.^[13] By comparison with the work of Robin et



Scheme 5. Hydrogenolysis of epoxide **11a**. Reagents and conditions: (a) H_2 , $\text{Pd}(\text{OH})_2$, THF , room temperature, 2 h (70%).

al.,^[14] we anticipated that this esterification could be achieved with compound **23**, which possesses a smaller steric effect. It would give an epoxycephalotaxine intermediate, which could be opened with nucleophiles to give natural esters of cephalotaxine. This strategy is under investigation in our laboratory.

Conclusions

The side-chains of esters of cephalotaxine are very important because they are responsible for the bioactivity and particularly the antileukemic activity of *Cephalotaxus* alkaloids. Several methods have been reported for the individual synthesis of these compounds, but only a few of them are general and enantioselective. In this paper we have described a straightforward and effective synthesis of monoacid side-chains of different natural esters of this family by the ring-opening of the chiral nonracemic functionalized epoxide **11a** with different organocuprates as nucleophiles. This epoxide, which represents the key intermediate in our procedure, was easily prepared from commercially available monomethyl itaconate (**8**). Unfortunately, the side-chains of harringtonine and homoharringtonine have not so far been obtained by this methodology, but efforts are being made to synthesize them.

Experimental Section

General: Reagents were commercially obtained at the highest commercial quality and used without further purification. All reactions were carried out under anhydrous conditions under argon or nitrogen in dry, freshly distilled solvents. Reactions were monitored by thin-layer chromatography on Merck 60F-254 precoated silica (0.2 mm) on aluminium. Flash chromatography was performed with SDS silica gel 60 (35–70 μm). Melting points were determined with a Kofler apparatus and are uncorrected. Specific rotations were measured at 25 °C with a Perkin-Elmer 341 polarimeter with a sodium (589 nm) lamp. IR spectra were recorded with a Nicolet 205 spectrometer and NaCl pellets. Only noteworthy IR absorptions are listed. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance-300 apparatus operating at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm.

1-[(1*S*)-2-Methoxy-2-oxo-1-phenylethyl] 4-Methyl 2-Methylidenebutanedioate (10**):** DCC (4.99 g, 24.2 mmol) and DMAP (2.96 g, 24.2 mmol) were added to a solution of methyl (*S*)-mandelate (**9**; 2.01 g, 12.1 mmol) and monomethyl itaconate (**8**) (2.62 g, 18.1 mmol) in anhydrous CH_2Cl_2 (40 mL). The mixture was stirred at room temperature for 5 h. The reaction mixture was then filtered

through a Celite® pad. The filtrate was washed (3×) with a saturated solution of NH₄Cl. The aqueous layer was extracted with CH₂Cl₂. The combined organic phases were washed (2×) with brine, dried with MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (cyclohexane/AcOEt, 4:1) to afford the alkene **10** (3.394 g, 96% yield) as a colorless oil. $[\alpha]_D^{25} = +118$ ($c = 1.0$, CHCl₃). IR (film): $\tilde{\nu} = 2954$ (CH), 1743 (C=O), 1642 (C=C), 1498, 1455, 1436 (Ar) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): $\delta = 3.40$ (t, $J = 1.2$ Hz, 2 H, 3-H), 3.65 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 5.83 (td, $J = 0.8$, 1.2 Hz, 1 H, 5a-H), 5.99 (s, 1 H, 6-H), 6.49 (d, $J = 0.8$ Hz, 1 H, 5b-H), 7.36–7.43 (m, 3 H, Ar-H), 7.44–7.50 (m, 2 H, Ar-H) ppm. ¹³C NMR (CDCl₃, 75 MHz): $\delta = 37.5$ (C-3), 52.1 (OMe), 52.7 (OMe), 74.9 (C-6), 127.6 (C-*o*), 128.8 (C-*m*), 129.3 (C-*p*), 130.1 (C-5), 132.9 (C-2), 133.7 (C-*i*), 165.3 (C-1), 169.0 (C-4), 170.8 (C-7) ppm. HRMS (ESI): calcd. for C₁₅H₁₆O₆ [M + Na]⁺ 315.0845; found 315.0838.

(1S)-2-Methoxy-2-oxo-1-phenylethyl (2S)- and (2R)-2-(2-Methoxy-2-oxoethyl)oxirane-2-carboxylate (11a and 11b): 2,4,6-Tri-*tert*-butylphenol (44 mg, 2% w/w of *m*-CPBA) and *m*-CPBA (2.21 g, 12.8 mmol, >95% purity^[8]) were successively added to a solution of the alkene **10** (1.872 g, 6.4 mmol) in 1,2-dichloroethane (32 mL). The mixture was stirred at 85 °C for 16 h. After cooling, the reaction mixture was diluted with CH₂Cl₂ and poured into a saturated and well-stirred solution of Na₂SO₃. Then powdered NaHCO₃ was added in portions until the release of gas had ceased. The organic and aqueous layers were separated. The aqueous phase was extracted with CH₂Cl₂ (3×30 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃ (3×100 mL) and brine, dried with MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (cyclohexane/AcOEt, 7:3) to give the epoxides **11a** and **11b** (1.414 g, 72% global yield) as an equimolar mixture. The diastereomers were isolated as colorless oils after a second silica gel column chromatography (pentane/Et₂O, 3:1).

Diastereomer 11a: 30% yield. $[\alpha]_D^{25} = +95.5$ ($c = 1.1$, CHCl₃). IR (film): $\tilde{\nu} = 2956$ (CH), 1747 (C=O), 1497, 1455, 1438 (Ar) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.82$ (d, $J = 16.9$ Hz, 1 H, 4a-H), 2.95 (d, $J = 5.8$ Hz, 1 H, 3a-H), 3.07 (d, $J = 16.9$ Hz, 1 H, 4b-H), 3.24 (d, $J = 5.8$ Hz, 1 H, 3b-H), 3.64 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 6.00 (s, 1 H, 7-H), 7.36–7.46 (m, 5 H, Ar-H) ppm. ¹³C NMR (CDCl₃, 75 MHz): $\delta = 37.4$ (C-4), 52.3 (C-3), 52.9 (OMe), 53.6 (C-2), 75.5 (C-7), 127.7 (C-*o*), 129.0 (C-*m*), 129.6 (C-*p*), 133.2 (C-*i*), 168.5 (C-5), 168.8 (C-8), 169.6 (C-6) ppm. HRMS (ESI): calcd. for C₁₅H₁₆O₇ [M + Na]⁺ 331.0794; found 331.0809.

Diastereomer 11b: 35% yield. $[\alpha]_D^{25} = +113.0$ ($c = 1.0$, CHCl₃). IR (film): $\tilde{\nu} = 2956$ (CH), 1747 (C=O), 1498, 1456, 1438 (Ar) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.80$ (d, $J = 16.9$ Hz, 1 H, 4a-H), 2.97 (d, $J = 5.9$ Hz, 1 H, 3a-H), 3.12 (d, $J = 16.9$ Hz, 1 H, 4b-H), 3.36 (d, $J = 5.9$ Hz, 1 H, 3b-H), 3.69 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 5.99 (s, 1 H, 7-H), 7.35–7.47 (m, 5 H, Ar-H) ppm. ¹³C NMR (CDCl₃, 75 MHz): $\delta = 37.1$ (C-4), 52.0 (C-3), 52.2 (OMe), 52.8 (OMe), 53.6 (C-2), 75.2 (C-7), 127.6 (C-*o*), 128.9 (C-*m*), 129.5 (C-*p*), 133.0 (C-*i*), 168.6 (C-5), 169.1 (C-8), 169.6 (C-6) ppm. HRMS (ESI): calcd. for C₁₅H₁₆O₇ [M + Na]⁺ 331.0794; found 331.0798.

General Procedure for the Epoxide Ring-Opening with Organocuprates: A solution of the relevant lithium compound (3 equiv.) in Et₂O was added dropwise to a cooled suspension of CuI (1.5 equiv.) in Et₂O at –78 °C. The temperature was progressively increased to –60 °C for 1.5 h. Then the black solution was recooled to –78 °C, and the epoxide **11a** (1 equiv.) dissolved in Et₂O was

slowly added. After 2 h of stirring at –78 °C, saturated ammonium chloride solution was added to the reaction mixture. At room temperature the resulting aqueous and organic layers were diluted with water and CH₂Cl₂ and then separated. The aqueous phase was extracted with CH₂Cl₂ (3×). The combined organic extracts were washed with brine, dried with MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography to give the ring-opened compound.

1-[1(S)-2-Methoxy-2-oxo-1-phenylethyl] 4-Methyl (2R)-2-Hydroxy-2-(3-methylbutyl)butanedioate (12): Obtained from a 0.85 M solution of 2-methylpropyllithium (3.16 mL, 2.68 mmol) in Et₂O (prepared from 1-bromo-2-methylpropane and lithium at 0 °C), a suspension of CuI (256 mg, 1.34 mmol) in Et₂O (9 mL), and epoxide **11a** (276 mg, 0.895 mmol) dissolved in Et₂O (2 mL). Chromatography (cyclohexane/AcOEt, 4:1) afforded the ring-opened product **12** (212 mg, 65% yield) as a colorless oil. $[\alpha]_D^{25} = +82.8$ ($c = 0.75$, CHCl₃). IR (film): $\tilde{\nu} = 3521$ (OH), 2956 (CH), 1747 (C=O), 1498, 1456, 1438 (Ar) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): $\delta = 0.90$ (d, $J = 6.6$ Hz, 3 H, 8-H), 0.91 (d, $J = 6.6$ Hz, 3 H, 9-H), 1.16–1.31 (m, 1 H, 7-H), 1.32–1.47 (m, 1 H, 6a-H), 1.47–1.63 (m, 1 H, 6b-H), 1.67–1.94 (m, 2 H, 5a-H, 5b-H), 2.71 (d, $J = 16.3$ Hz, 1 H, 3a-H), 2.92 (d, $J = 16.3$ Hz, 1 H, 3b-H), 3.53 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.73 (s, 1 H, OH), 5.99 (s, 1 H, 10-H), 7.30–7.45 (m, 5 H, Ar-H) ppm. ¹³C NMR (CDCl₃, 75 MHz): $\delta = 22.5$, 22.6 (C-8 and C-9), 28.2 (C-7), 31.5 (C-6), 37.2 (C-5), 43.3 (C-3), 51.8 (OMe), 52.6 (OMe), 75.2 (C-2), 75.3 (C-10), 127.6 (C-*o*), 128.8 (C-*m*), 129.4 (C-*p*), 133.5 (C-*i*), 168.7 (C-4), 171.1 (C-11), 174.6 (C-1) ppm. HRMS (ESI): calcd. for C₁₉H₂₆O₇ [M + Na]⁺ 389.1576; found 389.1587.

1-[1(S)-2-Methoxy-2-oxo-1-phenylethyl] 4-Methyl (2R)-2-Hydroxy-2-(4-methylpentyl)butanedioate (13): Obtained from a 0.89 M solution of 3-methylbutyllithium (3.28 mL, 2.92 mmol) in Et₂O (prepared from 1-bromo-3-methylbutane and lithium at 0 °C), a suspension of CuI (278 mg, 1.46 mmol) in Et₂O (9.5 mL), and epoxide **11a** (300 mg, 0.973 mmol) dissolved in Et₂O (2 mL). Chromatography (cyclohexane/AcOEt, 4:1) afforded the ring-opened product **13** (269 mg, 73% yield) as a colorless oil. $[\alpha]_D^{25} = +70.9$ ($c = 0.38$, CHCl₃). IR (film): $\tilde{\nu} = 3516$ (OH), 2954 (CH), 1748 (C=O), 1498, 1456, 1438 (Ar) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): $\delta = 0.87$ (d, $J = 6.6$ Hz, 6 H, 9-H, 10-H), 1.14–1.26 (m, 2 H, 7-H), 1.26–1.44 (m, 1 H, 8-H), 1.44–1.63 (m, 2 H, 6-H), 1.66–1.91 (m, 2 H, 5-H), 2.71 (d, $J = 16.3$ Hz, 1 H, 3a-H), 2.92 (d, $J = 16.3$ Hz, 1 H, 3b-H), 3.54 (s, 3 H, OMe), 3.71 (s, 1 H, OH), 3.72 (s, 3 H, OMe), 5.99 (s, 1 H, 11-H), 7.35–7.45 (m, 5 H, Ar-H) ppm. ¹³C NMR (CDCl₃, 75 MHz): $\delta = 20.7$ (C-6), 22.6, 22.7 (C-9 and C-10), 27.9 (C-8), 39.0 (C-5), 39.6 (C-7), 43.2 (C-3), 51.8 (OMe), 52.7 (OMe), 75.2 (C-2), 75.4 (C-11), 127.7 (C-*o*), 128.9 (C-*m*), 129.4 (C-*p*), 133.5 (C-*i*), 168.7 (C-4), 171.2 (C-12), 174.7 (C-1) ppm. HRMS (ESI): calcd. for C₂₀H₂₈O₇ [M + Na]⁺ 403.1733; found 403.1734.

1-[1(S)-2-Methoxy-2-oxo-1-phenylethyl] 4-Methyl (2R)-2-Benzyl-2-hydroxybutanedioate (16): Obtained from a 1.18 M commercial solution of phenyllithium (2.29 mL, 2.72 mmol) in dibutyl ether, a suspension of CuI (253 mg, 1.33 mmol) in Et₂O (7 mL), and epoxide **11a** (205 mg, 0.665 mmol) dissolved in Et₂O (2 mL). The cuprate formed after 30 min of stirring at 0 °C. After addition of the epoxide, the temperature was increased from –78 to –40 °C. Chromatography (cyclohexane/AcOEt, 4:1) afforded the ring-opened product **16** (127 mg, 50% yield) as a colorless oil. $[\alpha]_D^{25} = +61.0$ ($c = 0.4$, CHCl₃). IR (film): $\tilde{\nu} = 3535$ (OH), 3020, 2956 (CH), 1747 (C=O), 1497, 1456, 1439 (Ar) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.66$ (d, $J = 16.4$ Hz, 1 H, 3a-H), 3.01 (d, $J = 16.4$ Hz, 1 H, 3b-H), 3.06 (d, $J = 13.7$ Hz, 1 H, 5a-H), 3.19 (d, J

= 13.7 Hz, 1 H, 5b-H), 3.51 (s, 3 H, OMe), 3.75 (s, 4 H, OMe, OH), 6.01 (s, 1 H, 6-H), 7.23–7.33 (m, 5 H, Ar-H), 7.36–7.47 (m, 5 H, Ar-H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): δ = 42.4 (C-3), 45.0 (C-5), 51.9 (OMe), 52.8 (OMe), 75.4 (C-6), 75.5 (C-2), 127.2 (C-*p'*), 127.8 (C-*o*), 128.3 (C-*m'*), 128.9 (C-*m*), 129.5 (C-*p*), 130.8 (C-*o'*), 133.5 (C-*i*), 134.6 (C-*i'*), 168.8 (C-4), 171.1 (C-7), 174.0 (C-1) ppm. HRMS (ESI): calcd. for $\text{C}_{21}\text{H}_{22}\text{O}_7$ [$\text{M} + \text{Na}$] $^+$ 409.1263; found 409.1261.

1-[(1S)-2-Methoxy-2-oxo-1-phenylethyl] 4-Methyl (2R)-2-Hydroxy-2-pentylbutanedioate (18): Obtained from a 2.15 M commercial solution of butyllithium (0.996 mL, 2.14 mmol) in hexane, a suspension of CuI (204 mg, 1.07 mmol) in Et_2O (7.5 mL), and epoxide **11a** (220 mg, 0.714 mmol) dissolved in Et_2O (2 mL). Chromatography (cyclohexane/AcOEt, 4:1) afforded the ring-opened product **18** (166 mg, 64% yield) as a colorless oil. $[\alpha]_D^{25}$ = +73.7 (c = 0.51, CHCl_3). IR (film): $\tilde{\nu}$ = 3521 (OH), 2955 (CH), 1747 (C=O), 1498, 1456, 1438 (Ar) cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ = 0.91 (t, J = 6.7 Hz, 3 H, 9-H), 1.26–1.44 (m, 5 H, 8-H, 7-H, 6a-H), 1.44–1.61 (m, 1 H, 6b-H), 1.70–1.95 (m, 2 H, 5-H), 2.73 (d, J = 16.3 Hz, 1 H, 3a-H), 2.94 (d, J = 16.3 Hz, 1 H, 3b-H), 3.55 (s, 3 H, OMe), 3.74 (s, 4 H, OMe, OH), 6.01 (s, 1 H, 10-H), 7.35–7.48 (m, 5 H, Ar-H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): δ = 14.0 (C-9), 22.5 (C-6), 22.5 (C-8), 31.9 (C-7), 39.3 (C-5), 43.2 (C-3), 51.8 (OMe), 52.7 (OMe), 75.2 (C-2), 75.3 (C-10), 127.6 (C-*o*), 128.9 (C-*m*), 129.4 (C-*p*), 133.5 (C-*i*), 168.7 (C-4), 171.2 (C-11), 174.6 (C-1) ppm. HRMS (ESI): calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_7$ [$\text{M} + \text{Na}$] $^+$ 389.1576; found 389.1564.

1-[(1S)-2-Methoxy-2-oxo-1-phenylethyl] 4-Methyl (2R)-2-Hydroxy-2-(3-methylbut-2-en-1-yl)butanedioate (20): Obtained from a 0.18 M solution of 2-methylprop-1-enyllithium (11.0 mL, 1.95 mmol) in Et_2O (prepared from 1-bromo-2-methylpropene and *tert*-butyllithium at -78°C), a suspension of CuI (185 mg, 0.973 mmol) in Et_2O (3.5 mL), and epoxide **11a** (200 mg, 0.649 mmol) dissolved in Et_2O (2 mL). Chromatography (cyclohexane/AcOEt, 4:1) afforded the ring-opened product **20** (130 mg, 55% yield) as a colorless oil. $[\alpha]_D^{25}$ = +65.3 (c = 0.86, CHCl_3). IR (film): $\tilde{\nu}$ = 3508 (OH), 2955 (CH), 1747 (C=O), 1497, 1462, 1438 (Ar), 1352 (C=C) cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ = 1.63 (s, 3 H, 8-H), 1.73 (s, 3 H, 9-H), 2.54 (d, J = 7.5 Hz, 2 H, 5-H), 2.72 (d, J = 16.4 Hz, 1 H, 3a-H), 2.94 (d, J = 16.4 Hz, 1 H, 3b-H), 3.53 (s, 3 H, OMe), 3.69 (s, 1 H, OH), 3.72 (s, 1 H, OMe), 5.24 (t, J = 7.5 Hz, 1 H, 6-H), 5.99 (s, 1 H, 10-H), 7.34–7.47 (m, 5 H, Ar-H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): δ = 18.1 (C-8), 26.1 (C-9), 38.0 (C-5), 42.2 (C-3), 51.8 (OMe), 52.7 (OMe), 75.3 (C-10), 75.4 (C-2), 116.7 (C-6), 127.7 (C-*o*), 128.9 (C-*m*), 129.4 (C-*p*), 133.5 (C-*i*), 136.8 (C-7), 168.7 (C-4), 171.2 (C-11), 174.3 (C-1) ppm. HRMS (ESI): calcd. for $\text{C}_{19}\text{H}_{24}\text{O}_7$ [$\text{M} + \text{Na}$] $^+$ 387.1432; found 387.1420.

(1S)-2-Methoxy-2-oxo-1-phenylethyl (2R)-2-(2-Methoxy-2-oxoethyl)-5,5-dimethyltetrahydrofuran-2-carboxylate (21): Mercury diacetate [$\text{Hg}(\text{OAc})_2$; 116 mg, 0.364 mmol] was added to a solution of compound **20** (102 mg, 0.28 mmol) in a 1:1 mixture of THF/ H_2O (1.4 mL) cooled to 0°C . The mixture was warmed to room temperature and stirred for 2.5 h. Then NaBH_4 (21 mg, 0.570 mmol) dissolved in a 1 M NaOH solution (0.310 mL) was added dropwise. Following the release of gas and precipitation of mercury, the organic layer was diluted with THF. A saturated solution of NaCl was introduced, and the layers were separated. The aqueous phase was neutralized with a 1 M HCl solution and then extracted with AcOEt (3 $\times$). The combined extracts were washed with brine, dried with MgSO_4 , filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (cyclohexane/AcOEt, 4:1) to give the tetrahydrofuran **21** (78 mg, 76% yield) as a colorless oil. $[\alpha]_D^{25}$ = +50.0 (c = 1.15,

CHCl_3). IR (film): $\tilde{\nu}$ = 2956, 2926 (CH), 1747 (C=O), 1498, 1455, 1435 (Ar) cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ = 1.25 (s, 3 H, 11-H), 1.36 (s, 3 H, 12-H), 1.76–1.98 (m, 2 H, 4-H), 2.26 (ddd, J = 7.8, 8.8, 13.1 Hz, 1 H, 3a-H), 2.63 (ddd, J = 5.1, 7.4, 13.1 Hz, 1 H, 3b-H), 2.78 (d, J = 15.5 Hz, 1 H, 6a-H), 2.97 (d, J = 15.5 Hz, 1 H, 6b-H), 3.55 (s; 3 H, OMe), 3.70 (s, 1 H, OMe), 5.96 (s, 1 H, 9-H), 7.30–7.49 (m, 5 H, Ar-H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): δ = 28.3 (C-11), 29.0 (C-12), 35.6 (C-3), 37.6 (C-4), 43.7 (C-6), 51.8 (OMe), 52.7 (OMe), 74.8 (C-9), 83.7 (C-5), 84.5 (C-2), 127.7 (C-*o*), 128.8 (C-*m*), 129.3 (C-*p*), 133.7 (C-*i*), 169.2 (C-7), 170.3 (C-10), 172.9 (C-8) ppm. HRMS (ESI): calcd. for $\text{C}_{19}\text{H}_{24}\text{O}_7$ [$\text{M} + \text{Na}$] $^+$ 387.1420; found 387.1427.

General Procedure for the Hydrogenolysis of the Chiral Auxiliary: Under nitrogen, the substrate was dissolved in AcOEt (c = 0.035 M). Then 10% palladium on charcoal was added (mass of substrate/mass of catalyst = 1.8). The reaction was conditioned under hydrogen with stirring at room temperature for 4–5 h. Then it was filtered through a Celite[®] pad. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to yield the acid compound.

(2R)-2-Hydroxy-2-(2-methoxy-2-oxoethyl)-6-methylheptanoic Acid (14): Obtained from the ester **12** (504 mg, 1.375 mmol) in AcOEt (40 mL) with 10% Pd/C (280 mg). Silica gel column chromatography (CH_2Cl_2 then $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5) afforded the acid compound **14** (296 mg, 95% yield) as a colorless oil. $[\alpha]_D^{25}$ = –22.3 (c = 0.73, CHCl_3). IR (film): $\tilde{\nu}$ = 3600–2300, 3500 (COOH, OH), 2956 (CH), 1739 (C=O) cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ = 0.85 (d, J = 6.6 Hz, 3 H, 8-H), 0.85 (d, J = 6.6 Hz, 3 H, 9-H), 1.00–1.16 (m, 1 H, 7-H), 1.28–1.42 (m, 1 H, 6a-H), 1.42–1.56 (m, 1 H, 6b-H), 1.61–1.80 (m, 2 H, 5a-H, 5b-H), 2.72 (d, J = 16.5 Hz, 1 H, 3a-H), 2.96 (d, J = 16.5 Hz, 1 H, 3b-H), 3.67 (s, 3 H, OMe), 7.28 (br. s, 2 H, OH, COOH) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): δ = 22.4, 22.5 (C-8 and C-9), 28.1 (C-7), 31.8 (C-6), 37.1 (C-5), 43.0 (C-3), 52.1 (OMe), 75.2 (C-2), 171.8 (C-4), 179.4 (C-1) ppm. HRMS (ESI): calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_5$ [$\text{M} + \text{Na}$] $^+$ 241.1052; found 241.1051.

(2R)-2-Hydroxy-2-(2-methoxy-2-oxoethyl)-6-methylheptanoic Acid (15): Obtained from the ester **13** (491 mg, 1.29 mmol) in AcOEt (40 mL) with 10% Pd/C (275 mg). Silica gel column chromatography (CH_2Cl_2 then $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5) afforded the acid compound **15** (276 mg, 92% yield) as a white solid. $[\alpha]_D^{25}$ = –15.8 (c = 0.57, CHCl_3). M.p. $<50^\circ\text{C}$. IR (film): $\tilde{\nu}$ = 3600–2400, 3494 (COOH, OH), 2956 (CH), 1738 (C=O) cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ = 0.85 (d, J = 6.6 Hz, 6 H, 9-H, 10-H), 1.10–1.20 (m, 2 H, 7-H), 1.20–1.32 (m, 1 H, 8-H), 1.42–1.60 (m, 2 H, 6-H), 1.60–1.80 (m, 2 H, 5-H), 2.73 (d, J = 16.6 Hz, 1 H, 3a-H), 2.98 (d, J = 16.6 Hz, 1 H, 3b-H), 3.70 (s, 3 H, OMe), 8.15 (br. s, 2 H, OH, COOH) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): δ = 21.0 (C-6), 22.6, 22.7 (C-9 and C-10), 27.9 (C-8), 38.8 (C-5), 39.3 (C-7), 42.8 (C-3), 52.2 (OMe), 75.3 (C-2), 172.0 (C-4), 179.4 (C-1) ppm. HRMS (ESI): calcd. for $\text{C}_{11}\text{H}_{20}\text{O}_5$ [$\text{M} + \text{Na}$] $^+$ 255.1208; found 255.1205.

(2R)-2-Hydroxy-2-(2-methoxy-2-oxoethyl)heptanoic Acid (19): Obtained from the ester **18** (161 mg, 0.439 mmol) in AcOEt (12.5 mL) with 10% Pd/C (89 mg). Silica gel column chromatography (CH_2Cl_2 then $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5) gave the acid compound **19** (88 mg, 92% yield) as a colorless oil. $[\alpha]_D^{25}$ = –8.7 (c = 0.64, CHCl_3). IR (film): $\tilde{\nu}$ = 3700–2300, 3500 (COOH, OH), 2956, 2931 (CH), 1736 (C=O) cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ = 0.86 (t, J = 6.7 Hz, 3 H, 9-H), 1.14–1.36 (m, 5 H, 8-H, 7-H, 6a-H), 1.39–1.56 (m, 1 H, 6b-H), 1.60–1.80 (m, 2 H, 5-H), 2.72 (d, J = 16.6 Hz, 1 H, 3a-H), 2.97 (d, J = 16.6 Hz, 1 H, 3b-H), 3.68 (s, 3 H, OMe) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): δ = 14.0 (C-9), 22.5 (C-6), 22.8 (C-8), 31.8 (C-7), 39.1 (C-5), 42.9 (C-3), 52.1 (OMe), 75.3 (C-2),

171.9 (C-4), 179.3 (C-1) ppm. HRMS (ESI): calcd. for $C_{10}H_{18}O_5$ $[M + Na]^+$ 241.1052; found 241.1047.

(2R)-2-(2-Methoxy-2-oxoethyl)-5,5-dimethyltetrahydrofuran-2-carboxylic Acid (22): Obtained from the ester **21** (117 mg, 0.321 mmol) in AcOEt (9 mL) with 10% Pd/C (65 mg). Silica gel column chromatography (CH_2Cl_2 then $CH_2Cl_2/MeOH$, 95:5) afforded the acid compound **22** (62 mg, 90% yield) as a white solid. $[a]_D^{25} = -23.0$ ($c = 0.45$, $CHCl_3$). M.p. 83 °C. IR (film): $\tilde{\nu} = 3600\text{--}2700$, 3475 (COOH, OH), 2982 (CH), 1747, 1731 (C=O) cm^{-1} . 1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.29$ (s, 3 H, 9-H), 1.37 (s, 3 H, 10-H), 1.86 (t, $J = 7.2$ Hz, 2 H, 4a-H, 4b-H), 2.20 (ddd, $J = 7.4$, 7.6, 13.3 Hz, 1 H, 3a-H), 2.42 (ddd, $J = 6.9$, 7.1, 13.3 Hz, 1 H, 3b-H), 2.67 (d, $J = 15.8$ Hz, 1 H, 6a-H), 3.10 (d, $J = 15.8$ Hz, 1 H, 6b-H), 3.67 (s; 3 H, OMe), 8.21 (br. s, 1 H, COOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 28.5$ (C-9), 28.7 (C-10), 36.1 (C-3), 37.6 (C-4), 43.7 (C-6), 52.1 (OMe), 84.1 (C-5), 85.7 (C-2), 170.2 (C-7), 176.5 (C-8) ppm. HRMS (ESI): calcd. for $C_{10}H_{16}O_5$ $[M + Na]^+$ 239.0895; found 239.0899.

(2R)-2-Benzyl-2-hydroxy-4-methoxy-4-oxobutanoic Acid (17): Obtained after 24 h from the ester **16** (32 mg, 0.083 mmol) in AcOEt (5 mL; $c = 0.017$ M) with 20% palladium hydroxide $[Pd(OH)_2]$; 47 mg] and under 5 bar of hydrogen in a Parr apparatus. Silica gel column chromatography (CH_2Cl_2 then $CH_2Cl_2/MeOH$, 95:5) provided the acid compound **17** (16 mg, 85% yield) as a colorless oil. $[a]_D^{25} = -20.3$ ($c = 0.58$, $CHCl_3$). IR (film): $\tilde{\nu} = 3600\text{--}2500$, 3480 (COOH, OH), 2957, 2927 (CH), 1743, 1732 (C=O) cm^{-1} . 1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.70$ (d, $J = 16.6$ Hz, 1 H, 3a-H), 2.96 (d, $J = 13.5$ Hz, 1 H, 5a-H), 3.05 (d, $J = 16.6$ Hz, 1 H, 3b-H), 3.08 (d, $J = 13.5$ Hz, 1 H, 5b-H), 3.66 (s, 3 H, OMe), 5.65 (br. s, 2 H, OH, COOH), 7.19–7.33 (m, 5 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 42.2$ (C-3), 45.0 (C-5), 52.3 (OMe), 75.8 (C-2), 127.4 (C-p), 128.4 (C-m), 130.6 (C-o), 134.6 (C-i), 172.0 (C-4), 178.2 (C-1) ppm. HRMS (ESI): calcd. for $C_{12}H_{14}O_5$ $[M + Na]^+$ 261.0729; found 261.0739.

(2S)-2-(2-Methoxy-2-oxoethyl)oxirane-2-carboxylic Acid (23): $Pd(OH)_2$ (0.030 g) in anhydrous THF (10 mL) was placed in a two-necked round-bottomed flask under nitrogen. The reaction was conditioned under hydrogen. Then epoxide **11a** (0.100 g, 0.325 mmol) dissolved in anhydrous THF (2 mL) was added, and the solution was stirred at room temperature and atmospheric pressure for 2 h. The reaction mixture was then filtered through a Celite® pad. The filtrate was concentrated under reduced pressure. The crude product was washed with saturated aqueous $NaHCO_3$, the aqueous layer was then acidified with 0.1 M aqueous hydrochloric acid, and extracted with ethyl acetate. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. This treatment afforded the epoxide **23** (0.036 g, 70% yield) as a colorless oil. IR (film): $\tilde{\nu} = 3486$, (COOH), 2957 (CH_3), 2856 (CH_2), 1743 (C=O) cm^{-1} . 1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.75$ (d, $J = 17.16$ Hz, 1 H, 4a-H), 3.00 (d, $J = 5.51$ Hz, 1 H, 3a-H), 3.15 (d, $J = 17.17$ Hz, 1 H, 4b-H), 3.25 (d, $J = 5.49$ Hz, 1 H, 3b-H), 3.77 (s, 3 H, OMe), 6.9 (br. s, 1 H, COOH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 36.83$ (C-4), 52.06 (C-3), 52.34 (OMe), 53.58 (C-2), 169.80 (C-5), 173.85 (C-6) ppm. HRMS (ESI): calcd. for $C_6H_8O_5$ $[M + Na]^+$ 183.0263; found 183.0269.

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- [1] a) H. Itokawa, X. Wang, K.-H. Lee, in *Anticancer Agents from Natural Products* (Eds.: G. H. Cragg, D. G. I. Kingston, D. J. Newman), CRC Press, Boca Raton, FL, **2005**, pp. 47–70; b) J. L. Grem, B. D. Cheson, S. A. King, B. Leyland-Jones, M. Suffness, *J. Natl. Cancer Inst.* **1988**, *80*, 1095–1103; c) W. Tang, G. Eisenbrand (Eds.), “Cephalotaxus spp.” in *Chinese Drugs of Plant Origin, Chemistry, Pharmacology, and Use in Traditional and Modern Medicine*, Springer, Berlin, **1992**, pp. 281–306.
- [2] a) R. G. Powell, D. Weisleder, C. R. Smith Jr, W. K. Rohwedder, *Tetrahedron Lett.* **1970**, *11*, 815–818; b) for a review, see: M. A. Jilal Miah, T. Hudlicky, J. W. Reed in *The Alkaloids* (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, vol. 51, pp. 199–264.
- [3] For recent papers on clinical trials of homoharringtonine, see: a) H. M. Kantarjian, M. Talpaz, V. Santini, A. Murgo, B. Cheson, S. M. O'Brien, *Cancer* **2001**, *92*, 1591–1605; b) S. M. O'Brien, M. Talpaz, J. Cortes, J. Shan, F. J. Giles, S. Faderl, D. Thomas, G. Garcia-Manero, S. Mallard, M. B. Rios, C. Koller, S. Kornblau, M. Andreeff, A. Murgo, M. Keating, H. M. Kantarjian, *Cancer* **2002**, *94*, 2024–2032; c) B. Scappini, F. Onida, H. M. Kantarjian, L. Dong, S. Verstovsek, M. J. Keating, M. Beran, *Cancer* **2002**, *94*, 2653–2662; d) E. Hitt, *Lancet Oncol.* **2002**, *3*, 259; e) A. Quintas-Cardama, J. Cortes, *Expert Opin. Pharmacother.* **2008**, *9*, 1029–1037; f) W. G. Zhang, F. X. Wang, Y. X. Chen, X. M. Cao, A. L. He, J. Liu, X. R. Ma, W. H. Zhao, S. H. Liu, J. L. Wang, *Am. J. Hematol.* **2008**, *83*, 185–188.
- [4] a) W. W. Paudler, G. I. Kerley, J. McKay, *J. Org. Chem.* **1963**, *28*, 2194–2197; b) R. G. Powell, D. Weisleder, C. R. Smith Jr, I. A. Wolff, *Tetrahedron Lett.* **1969**, *10*, 4081–4084; c) D. J. Abraham, R. D. Rosenstein, E. L. McGandy, *Tetrahedron Lett.* **1969**, *10*, 4085–4086; d) S. K. Arora, R. B. Bates, R. A. Grady, R. G. Powell, *J. Org. Chem.* **1974**, *39*, 1269–1271; e) S. K. Arora, R. B. Bates, R. A. Grady, G. Germain, J. P. Declercq, R. G. Powell, *J. Org. Chem.* **1976**, *41*, 551–554.
- [5] a) S. Brandange, S. Josephson, S. Vallen, *Acta Chem. Scand.* **1974**, *28*, 153–156; b) S. Brandange, S. Josephson, S. Vallen, *Acta Chem. Scand.* **1973**, *27*, 3668–3672; c) S. Brandange, I. Granelli, B. Luning, C. Moberg, E. Sjostrand, *Acta Chem. Scand.* **1972**, *26*, 2558–2560; d) S. Brandange, B. Luning, *Acta Chem. Scand.* **1969**, *23*, 1151–1154; e) B. Luning, H. Trankner, S. Brandange, *Acta Chem. Scand.* **1966**, *20*, 2011; f) H. Kizu, E. Kaneko, T. Tomimori, *Chem. Pharm. Bull.* **1999**, *47*, 1618–1625.
- [6] a) T. R. Kelly, J. C. McKenna, P. A. Christenson, *Tetrahedron Lett.* **1973**, *14*, 3501–3504; b) L. Keller, F. Dumas, J. d'Angelo, *Eur. J. Org. Chem.* **2003**, 2488–2497; c) J. Auerbach, T. Ipakchi, S. M. Weinreb, *Tetrahedron Lett.* **1973**, *14*, 4561–4564; d) R. A. Ancliff, A. T. Russell, A. J. Sanderson, *Chem. Commun.* **2006**, 3243–3245.
- [7] S. A. A. El Bialy, H. Braun, L. F. Tietze, *Eur. J. Org. Chem.* **2005**, 2965–2972.
- [8] D. D. Perrin, W. L. F. Armarego in *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, **1988**, p. 123.
- [9] a) C. R. Johnson, R. W. Herr, D. M. Wieland, *J. Org. Chem.* **1973**, *38*, 4263–4268; b) H. M. Sirat, E. J. Thomas, J. D. Wallis, *J. Chem. Soc. Perkin Trans. 1* **1982**, 2885–2896.
- [10] a) H. Gilman, R. G. Jones, L. A. Woods, *J. Org. Chem.* **1952**, *17*, 1630–1634; b) B. H. Lipshutz, J. A. Kozlowski, R. S. Wilhelm, *J. Org. Chem.* **1983**, *48*, 546–550; c) N. R. Schmuff, B. M. Trost, *J. Org. Chem.* **1983**, *48*, 1404–1412.
- [11] a) M. Ohtani, T. Matsuura, F. Watanabe, M. Narisada, *J. Org. Chem.* **1991**, *56*, 4120–4123; b) J. L. Charlton, K. Koh, *J. Org. Chem.* **1992**, *57*, 1514–1516.
- [12] a) The same cyclization procedure was recently reported by Gin and co-workers in the preparation of anhydroharringtonine: J. D. Eckelbarger, J. T. Wilmot, M. T. Epperson, C. S. Thakur, D. Shum, C. Antczak, L. Tarassishin, H. Djaballah, D. Y. Gin,

- Chem. Eur. J.* **2008**, *14*, 4293–4306; b) hazards in handling mercuric acetate can be found in P. Kocovsky, J. Hofferberth, “Mercury(II) acetate” in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, p. 3242.
- [13] T. R. Kelly, R. W. McNutt Jr, M. Montury, N. P. Tosches, K. L. Mikolajczak, C. R. Smith Jr, D. Weisleder, *J. Org. Chem.* **1979**, *44*, 63–67.
- [14] J.-P. Robin, R. Dhal, G. Dujardin, L. Girodier, L. Mevellec, S. Poutot, *Tetrahedron Lett.* **1999**, *40*, 2931–2934.

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