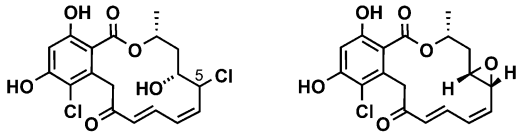
Natural Products Synthesis

Modular Asymmetric Synthesis of Pochonin C**

*Sofia Barluenga, Pilar Lopez, Emilie Moulin, and Nicolas Winssinger**

Dedicated to Professor Jean-Marie Lehn on the occasion of his 65th birthday

Pochonin C was isolated from a high-throughput screening program aimed at discovering novel antiviral agents against Herpes Simplex Virus (HSV).[1] Pochonin C (Scheme 1)



1: pochonin C **2**: radicicol (monorden)

Scheme 1. Structure of pochonin C (**1**) and radicicol (**2**).

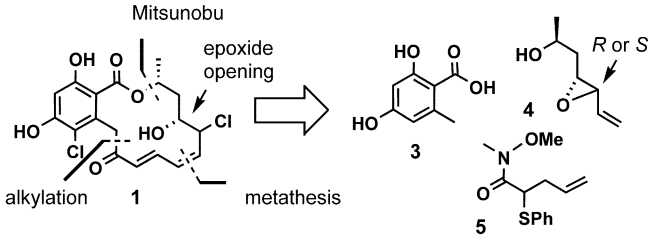
belongs to a family of six related macrolides (pochonins A–F) but attracted our attention by having the highest selectivity index (Tox_{50}/IC_{50}) against HSV amongst the pochonins and by being closely related to radicicol (also known as monorden),[2–4] a potent HSP90 inhibitor.[5] In fact, Hellwig et al. suggest that a formal ring opening of radicicol yields the chlorohydrin functionality of pochonin C. Nevertheless, the stereochemistry of C5 bearing the chlorine atom in pochonin C remains undefined. Although an HCl-promoted ring opening of radicicol has been described in the literature,[6] the two products have not been compared. Herein, we report the total synthesis of pochonin C and its conversion into radicicol.

The important therapeutic potential of HSP90 inhibition[7] and the structural relationship of pochonin C to radicicol motivated us to develop a synthesis that would be sufficiently concise to allow it to be mostly performed in a combinatorial fashion. A major criterion in such analysis is the commercial availability or ease of preparation of the fragments. Inspired by the previous work in the area,[8,9] we reasoned that the molecule could be disconnected into three fragments as shown in Scheme 2; both possible diastereoisomers of the C5 chlorine center would stem from the *cis*- or *trans*-epoxide moiety **4**. Given that ring-closing metathesis (RCM) of the conjugated diene could lead to four different products (12-

[*] Dr. S. Barluenga, Dr. P. Lopez, E. Moulin, Prof. N. Winssinger
Institut de Science et d'Ingénierie Supramoleculaires
Université Louis Pasteur
8 allée Gaspard Monge, 67000 Strasbourg (France)
Fax: (+33) 3-9024-5112
E-mail: winssinger@isis.u-strasbg.fr

[**] A Marie Curie Fellowship to S.B. (Grant no.: HPMF-CT-2002-01968) and Fellowships from the CNRS to P.L. and E.M. are gratefully acknowledged.

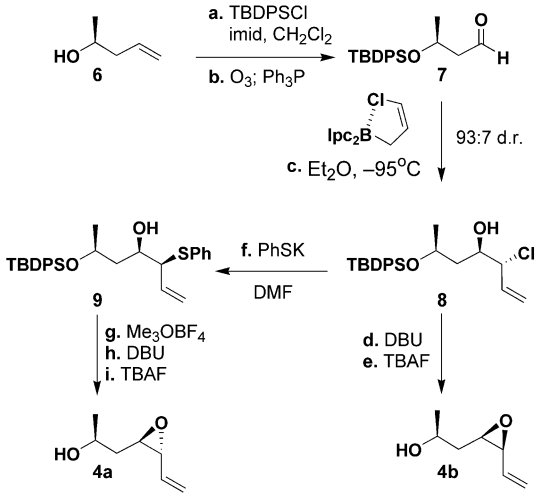
 DOI: 10.1002/ange.200454108



Scheme 2. Retrosynthetic disconections of pochonin C (**1**).

versus 14-membered ring and *cis*/*trans* isomers), it was reasoned that keeping the α,β-conjugated olefin masked as a thioether could prevent undesired cyclization to the 12-membered ring. The second element of control in the RCM was thought to be the timing of epoxide opening (before or after the RCM), which would offer some flexibility over the conformational organization of the open-chain system.

Both the *cis* and *trans* epoxides, **4a** and **b**, were accessed by a divergent strategy based on inversion of one of the epoxide stereocenters (Scheme 3). Thus, silyl protection of

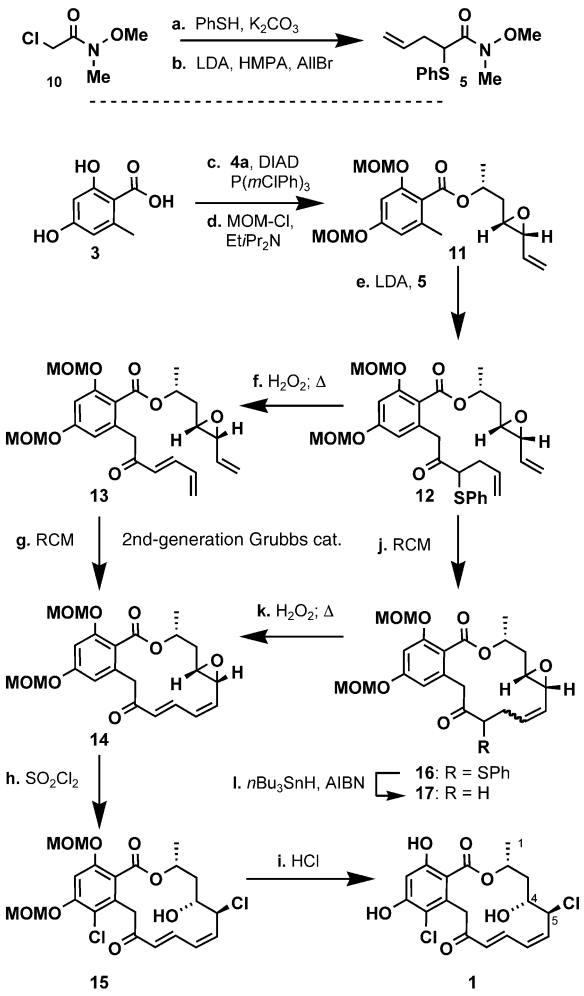


Scheme 3. Stereodivergent synthesis of alcohols **4a** and **4b**. a) TBDPSCl (1.1 equiv), imidazole (1.7 equiv), CH_2Cl_2, 23 °C, 4 h, 98%; b) O_3, CH_2Cl_2, −78 °C, 5 min; Ph_3P (1.5 equiv), 23 °C, 2 h, 94%; c) allyl chloride (2.0 equiv), LiN*c*Hex (2.0 equiv), IpcBOMe (1.5 equiv), BF_3OEt_2 (2.5 equiv), −95 °C, 4 h, 68% (93:7 d.r.); d) DBU (3.0 equiv), CH_2Cl_2, 0 °C, 8 h, 97%; e) TBAF (1.2 equiv), THF, 23 °C, 6 h, 98%; f) thiophenol (4.4 equiv), *t*BuOK (3.3 equiv), 23 °C, 1 h; then, **8** (1.0 equiv), DMF, 0→23 °C, 86%; g) Me_3OBF_4 (2.0 equiv), CH_2Cl_2, 0→23 °C, 4 h; h) DBU (3.0 equiv), CH_2Cl_2, 0 °C, 4 h, 80% (two steps); i) TBAF (1.2 equiv), THF, 23 °C, 6 h, 98%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, imid = imidazole, Ipc = isopinocampheyl, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl.

alcohol **6**[10,11] followed by ozonolysis afforded the protected aldehyde **7** in excellent yield. Modified Brown allylation with allyl chloride[12] yielded the halohydrin **8**, which was converted directly into the *cis* epoxide **4b** by the action of DBU and subsequent TBAF-induced deprotection. The corresponding *trans* epoxide **4a** was reached by S_N2 displacement of the chlorine atom with thiophenoxide to obtain compound **9**. The oxirane was then formed by activation of the thioether through methylation of the sulfur atom; this was followed by the addition of base to yield the corresponding *trans* epoxide. Removal of the silyl protecting group with TBAF led to the desired alcohol **4a**.[13]

The Weinreb amide **5** was obtained by displacement of the chloride center from **10**[10] with thiophenol and subsequent alkylation of the resulting product with allyl bromide in the presence of HMPA (Scheme 4).

Esterification of the dihydroxytoluic acid under Mitsunobu or carbodiimide conditions was found to work best when the 2-OH group was unprotected. Rather than manipulate protecting groups to access the suitably monoprotected dihydroxytoluic acid, we opted to investigate a selective Mitsunobu esterification of the unprotected acid **3**.[10] While the use of classical conditions (Ph_3P, DIAD, CH_2Cl_2, THF, or toluene)[14] gave poor selectivity between the desired esterification and undesired alkylation of the *para*-phenol, the use of tris(3-chlorophenyl)phosphane[15] gave the desired ester with greater than 95:5 selectivity and in good yield. Subsequent protection of the two phenol groups with MOMCl afforded toluic ester **11**. Deprotonation of the benzylic position[16] with LDA at −78 °C gave a deep red solution which was quenched with the Weinreb amide **5** to yield the cyclization precursor **12**. Notably, the reaction required 2 equivalents of LDA to proceed. Treatment of intermediate **12** with the second-generation Grubbs catalyst[17] in toluene at 120 °C[18] led to rapid ring closure and the formation of macrocycle **16** as an inseparable mixture of *cis* and *trans* olefins (1:1). The high yield of the reaction was gratifying as the β-thioether could potentially form a stable complex that would shut down the catalytic cycle.[19] Chemoselective oxidation of the thioether with H_2O_2 in hexafluoropropan-2-ol[20] led to clean conversion into the thiosulfoxide with no overoxidation product or epoxide opening, as had been observed with *meta*-chloroperoxybenzoic acid or H_2O_2/$ScOTf_3$ (Tf = trifluoromethanesulfonyl).[21] Interestingly, elimination of the sulfoxide proceeded *only* for the compound leading to the desired *trans*,*cis* diene **14**. Presumably, the *trans* olefin **16** cannot adopt an adequate conformation to participate in a 1,2-*syn* elimination of the sulfoxide group. Conversely, the thioether group could be removed under free radical conditions to obtain the dihydroradicicol macrocycle **17**. The selectivity in the elimination clearly suggested that carrying out the metathesis on diene **13** should lead to the desired *trans*,*cis* diene. Indeed oxidation/elimination of thioether **12** prior to ring closure followed by RCM at 120 °C led exclusively to the desired conjugated *trans*,*cis* diene **14** (Table 1) within 10 min. It has been shown that the *cis*/*trans* selectivity of the RCM in unsubstituted 14-membered macrocycles is kinetically controlled;[22] however, the high degree of selectivity in the ring closure of **13** cannot be attributed to the short reaction time considering the lack of selectivity for the closure of **12** under the same conditions. All that remained in order to reach pochonin C was the chlorination of the aryl ring and stereoselective opening of the epoxide. After investigating several reaction-sequence permutations, it was found that both operations could be carried out in a single step by using an excess of SO_2Cl_2 (no overchlorination of the



Scheme 4. Synthesis of pochonin C (**1**) from alcohol **4a**. a) PhSH (1.2 equiv), K_2CO_3 (1.5 equiv), DMF, 23 °C, 3 h, 98%; b) LDA (1.0 equiv), HMPA (1.0 equiv), AllBr (1.1 equiv), THF, −78→23 °C, 3 h, 82%; c) **4a** (1.0 equiv), P(*m*ClPh)$_3$ (2.0 equiv), DIAD (2.0 equiv), toluene, 23 °C, 3 h, 84%; d) MOMCl (4.0 equiv), DIPEA (4.0 equiv), TBAI (cat.), DMF, 80 °C, 3 h, 91%; e) LDA (2.0 equiv), THF, −78 °C, **5** (1.0 equiv), 81%; f) H_2O_2 (2.0 equiv), $(CF_3)_2CHOH$, 23 °C, 3 h; then, toluene, 80 °C, 1 h, 92%; g) second-generation Grubbs catalyst (5 mol%), toluene (2 mM), 120 °C, 10 min, 87%; h) SO_2Cl_2 (3.0 equiv), Et_2O, 0 °C, 68%; i) HCl (conc.; 2.5% in dioxane), 23 °C, 3 h, 74%; j) second-generation Grubbs catalyst (5 mol%), toluene (2 mM), 120 °C, 10 min, 94%; k) H_2O_2 (2.0 equiv), $(CF_3)_2CHOH$, 23 °C, 3 h; then, toluene, 80 °C, 1 h, 22% (85% based on recovered sulfoxide); l) nBu_3SnH (5.0 equiv), AIBN (cat.), toluene, microwave at 300 W, 10 min, 91%. AIBN = 2,2′-azobisisobutyronitrile, DIAD = diisopropylazodicarboxylate, DIPEA = diisopropylethylamine, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, MOM = methoxymethyl, second-generation Grubbs catalyst = [ruthenium{1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene}dichloro (phenylmethylene)(tricyclohexylphosphane)], TBAI = tetrabutylammonium iodide.

aromatic ring was observed).[8,23] Final deprotection of the MOM groups from **15** led to compound **1** (Table 1), which was found to have identical NMR spectra to pochonin C.[24] Importantly, treatment of compound **1** with K_2CO_3 led to rapid and clean oxirane formation to yield compound **2**, which was identical to radicicol (Scheme 5).

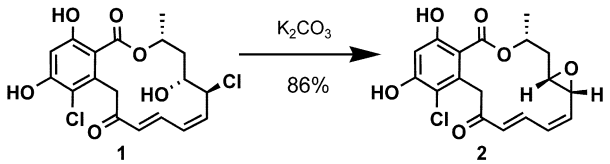
Table 1: Selected data for compounds **1**, **14**, **15**, and **19**.

1: R_f = 0.11 (SiO_2, EtOAc/cyclohexane (1:3)); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.28 (s, 1H), 8.59 (s, 1H), 7.11 (dd, 1H, J = 14.7, 12.3 Hz), 6.66 (s, 1H), 6.31 (t, 1H, J = 10.4 Hz), 6.10 (d, 1H, J = 16.1 Hz), 5.91 (m, 1H), 5.78 (t, 1H, J = 9.9 Hz), 5.22 (d, 1H, J = 15.8 Hz), 4.92 (t, 1H, J = 9.1 Hz), 3.96 (d, 1H, J = 15.8 Hz), 3.95 (m, 1H), 2.48 (dd, 1H, J = 15.8, 10.7 Hz), 2.13 (m, 1H), 1.54 ppm (d, 3H, J = 6.4 Hz); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.58 (s, 1H), 10.13 (s, 1H), 7.12 (dd, 1H, J = 16.1, 11.3 Hz), 6.56 (s, 1H), 6.27 (t, 1H, J = 10.8 Hz), 6.04 (d, 1H, J = 16.1 Hz), 5.78 (t, 1H, J = 10.8 Hz), 5.46 (d, 1H, J = 5.4 Hz), 5.28 (m, 1H), 5.10 (dd, 1H, J = 9.9, 4.8 Hz), 4.05 (d, 1H, J = 16.1 Hz), 3.99 (m, 1H), 3.60 (d, 1H, J = 16.1 Hz), 1.90–1.84 (m, 2H), 1.37 ppm (d, 3H, J = 6.2 Hz); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 25 °C): δ = 197.0, 166.5, 155.5, 139.1, 137.0, 133.2, 132.1, 129.9, 115.1, 112.2, 102.9, 71.1, 69.5, 60.8, 44.9, 37.8, 19.0 ppm; HRMS (ESI-TOF): calcd for $C_{18}H_{18}Cl_2O_6$ [M+Na$^+$]: 422.9995; found: 423.0337

14: R_f = 0.19 (SiO_2, EtOAc/cyclohexane (1:3)); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.68 (dd, 1H, J = 16.1, 11.3 Hz), 6.75 (d, 1H, J = 2.1 Hz), 6.59 (d, 1H, J = 2.1 Hz), 6.26 (t, 1H, J = 11.3 Hz), 6.05 (d, 1H, J = 16.1 Hz), 5.84 (dd, 1H, J = 10.8 Hz, 4.4 Hz), 5.42–5.33 (m, 1H), 5.21–5.17 (m, 2H), 5.14 (s, 2H), 3.97 (d, 1H, J = 14.0 Hz), 3.86 (d, 1H, J = 13.4 Hz), 3.57 (m, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 3.10–3.13 (ddd, 1H, J = 7.5, 3.7, 2.2 Hz), 2.47 (dt, 1H, J = 14.5, 4.8 Hz), 1.73 (ddd, 1H, J = 15.0, 7.5, 3.2 Hz), 1.59 ppm (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.9, 166.8, 159.2, 156.0, 140.2, 136.6, 134.5, 131.8, 130.2, 117.8, 108.7, 102.1, 94.6, 94.3, 69.8, 56.3, 55.8, 54.9, 42.4, 37.1, 29.7 18.9 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{26}O_8$ [M+Na$^+$]: 441.1520; found: 441.1595

15: R_f = 0.25 (SiO_2, EtOAc/cyclohexane (1:1)); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.18 (dd, 1H, J = 16.2, 11.2 Hz), 7.04 (s, 1H), 6.26 (t, 1H, J = 10.9 Hz), 6.10 (d, 1H, J = 16.4 Hz), 5.81 (t, 1H, J = 10.2 Hz), 5.47 (m, 1H), 5.35–5.12 (m, 6H), 4.11 (d, 1H, J = 15.8 Hz), 3.92 (d, 1H, J = 15.8 Hz), 3.56–3.48 (m, 2H), 3.55 (s, 3H), 3.53 (s, 3H), 1.57 ppm (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.3, 166.7, 159.3, 156.0, 140.8, 137.9, 134.7, 133.2, 131.2, 117.8, 102.0, 95.2, 94.6, 71.9, 69.7, 60.4, 56.7, 56.4, 45.1, 21.0, 18.8 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{26}Cl_2O_8$ [M+Na$^+$]: 510.9994; found: 511.0002

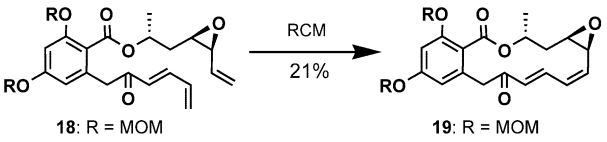
19: R_f = 0.19 (SiO_2, EtOAc/cyclohexane (1:3)); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.66 (dd, 1H, J = 15.8, 10.8 Hz), 6.75 (s, 1H), 6.58 (s, 1H), 6.25 (t, 1H, J = 9.7 Hz), 6.04 (d, 1H, J = 15.8 Hz), 5.83 (dd, 1H, J = 10.8 Hz, 4.3 Hz), 5.37 (m, 1H), 5.20–5.16 (m, 2H), 5.13 (s, 2H), 3.96 (d, 1H, J = 13.7 Hz), 3.85 (d, 1H, J = 13.7 Hz), 3.56 (br s, 1H), 3.48 (s, 3H), 3.46 (s, 3H), 3.11–3.09 (m, 1H), 2.49–2.42 (ddd, 1H, J = 15.2, 5.1, 4.3 Hz), 1.73–1.68 (ddd, 1H, J = 15.2, 7.2, 3.0 Hz), 1.58 ppm (d, 3H, J = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.8, 166.8, 159.2, 156.1, 140.1, 136.6, 132.8, 131.8, 130.2, 114.2, 108.7, 102.1, 94.6, 94.3, 69.8, 56.3, 55.7, 54.9, 42.4, 37.1, 29.7 18.8 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{26}O_8$ [M+Na$^+$]: 441.1520; found: 441.1599



Scheme 5. Conversion of pochonin C (**1**) into radicicol (**2**). K_2CO_3 (2.0 equiv), DMF, 23 °C, 1 h, 86%.

A similar reaction sequence starting from alcohol **4b** and toluic acid **3** led to the triene **18**. Treatment of this compound with the successful metathesis conditions used for **13** afforded

the ring-closure product **19** (Table 1) as the conjugated *trans*,*cis* diene, albeit in poor yield (Scheme 6).



18: R = MOM **19**: R = MOM

Scheme 6. Ring-closing metathesis with the *cis* epoxide stemming from alcohol **4b**. second-generation Grubbs catalyst (5 mol%), toluene (2 mM), 120°C, 10 min, 21%.

In conclusion, we have developed an expedient stereoselective synthesis of pochonin C and demonstrated the conversion of the product into radicicol, thereby assigning the stereochemistry of C5 as *S*. RCM has been used extensively for the synthesis of macrocyclic natural products,[25] but with some unpredictability in the stereochemical outcome.[26] There are, however, few examples of RCM for macrocycles with conjugated diene functionalities[27] that could potentially give rise to different modes of cyclization. The exceptionally selective RCM for the conversion of **13** into **14** testifies to the conformational restrictions of the radicicol macrocycles and adds a precedent for the feasibility of this transformation. The use of the described chemistry for the construction of combinatorial libraries is currently underway.

Received: February 26, 2004 [Z54108]

Keywords: asymmetric synthesis · conformation analysis · metathesis · natural products · total synthesis

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