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Convenient access to bis-indole alkaloids. Application to the synthesis of topsentins

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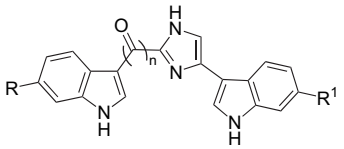
ABSTRACT

Topsentins and related bis-indole alkaloids may be efficiently synthesized through an addition/oxidation sequence leading to 2-(3-indolylcarbonyl)-imidazole derivatives followed by a Pd-catalyzed heteroarylation with the appropriate 3-stannylindoles.

1. Introduction

During the last two decades or so, a group of rare but structurally related bis-(indolyl)imidazole metabolites known as the topsentins[1] (Fig. 1) has established itself as a class of biologically important natural products.

Since the first report, in 1987,[1a] relating on the isolation of this class of compounds from marine sponges[1] the study of their biological activities has attracted considerable interest. Accordingly, remarkably diverse types of bioactivities such as antitumor,[1b,f,g] antiviral,[1b] antifungal,[1e] antibacterial,[1h] and anti-inflammatory[2] activities have been reported. Due to the important biological properties featuring this class of natural products its members were soon recognized as attractive candidates for studies aimed to the potential development of a new class of pharmacologically active agents, and therefore as interesting targets for synthetic developments. Among the strategies used for the few syntheses of this class of compounds two categories appear. Indeed, the tricyclic core has been built either through the construction of the central imidazole (or α-ketoimidazole) unit from two 3-indolyl-derivatives[1b,3] or by the binding of two 3-indolyl derivatives to a preformed imidazole (or α-ketoimidazole) moiety.[4] Moreover, basically two approaches have been developed within each category. For the building of the central imidazole unit, the pioneering approach involved the self-condensation of a 3-indolyl-glyoxaldimine derivative (intermediate generated in situ from 3-bromoacetylindole via an acetylhydrazinium derivative). It was developed for the first synthesis of deoxytopsentin **1**[3a] (Fig. 1), which appeared soon after the first paper on isolation and characterization of topsentin derivatives.[1a] Closely related self-[1b,3b] and cross-condensations[1b] have then been achieved by generating similar intermediates capable to condensate in situ. Accordingly, Rinehart reported the first synthesis of topsentin **2** (Fig. 1), albeit in low yield, via the cross-condensation of the intermediates generated from the action of ammonia on 3-glyoxalindole and 6-benzyloxy-3-glyoxalindole.[1b] On the other hand, it was recently shown that the central α-ketoimidazole unit of topsentins may be conveniently formed by condensation between a 3-indolyl-α,β-diaminoethane derivative and a 3-indolyl-α-ketoimidate.[3c,d] The first synthesis of



n = 1
1 R = R^1 = H Deoxytopsentin
2 R = OH, R^1 = H Topsentin
3 R = Br R^1 = Br Dibromodeoxytopsentin
4 R = H, R^1 = Br Deoxybromotopsentin
5 R = OH, R^1 = Br Bromotopsentin
n = 0
6 R = R^1 = H Nortopsentin D

Figure 1.

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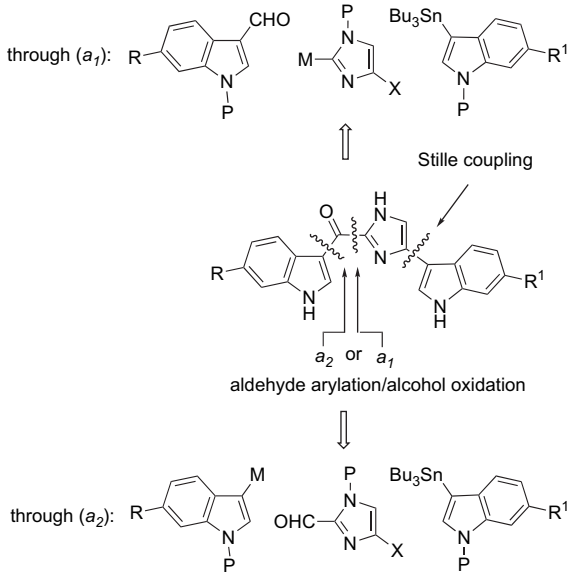
dibromodeoxytopsentin **3**[3d] (Fig. 1) along with other topsentin derivatives have been described in this way. Obviously this approach is more efficient for the synthesis of topsentin derivatives involving two different indolyl moieties than the above one that involves unselective cross-condensation reactions. With regard to the strategy based on the binding of two 3-indolyl derivatives to a preformed imidazole derivative, two similar approaches using palladium-catalyzed couplings were shown to work efficiently.[4] One was developed for both the first synthesis of nortopsentin D **6**[4a] (Fig. 1) and the synthesis of topsentin **2**.[4b] The synthesis of **2** made use of the Suzuki reaction[5] between the indolyl residue and the imidazole unit. Then the indolylcarbonyl moiety was incorporated via organometallic addition of the intermediate to a (3-indolyl)-Weinreb amide. For the synthesis of **6**, both indolyl residues were linked to the imidazole unit by successive Suzuki couplings. The other approach also involved the assembly of the topsentin framework by successively forming two carbon–carbon bonds as retrosynthetically depicted in Scheme 1, i.e., an aryl–aryl (5-imidazolyl, 3-indolyl) bond via a Stille coupling[6] and a C–C(O) bond via aldehyde-arylation followed by oxidation of the secondary alcohol. The last two-step sequence may be performed starting from an aldehyde situated either on the indole moiety or on the imidazole ring, thus forming a 2-(imidazolyl)–carbonyl bond (option a_1 in Scheme 1) or a 3-(indolyl)–carbonyl bond (option a_2 in Scheme 1), respectively.

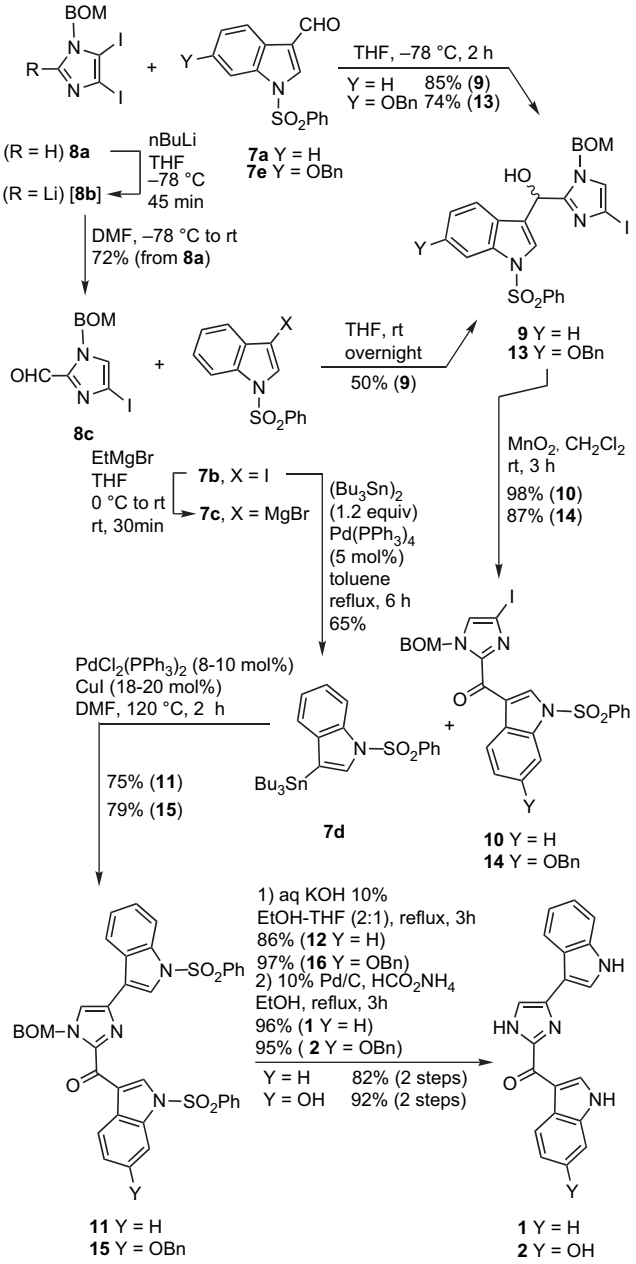


Scheme 1. Retrosynthetic scheme.

Some time ago, we have reported the syntheses of deoxytopsentin **1** and topsentin **2** through route a_1, and the first syntheses of deoxybromotopsentin **4** and bromotopsentin **5** (Fig. 1) following the alternative route a_2.[4c] Our approach is versatile allowing a convenient access to all members of the topsentin family from simple and easily available commercial starting materials providing satisfactory yields, equivalent or even higher than those delivered through different approaches. The upsurge of recent papers devoted to the study of new syntheses and pharmacological properties of topsentins[1j,3c,d] and related bis-indole alkaloids[7] bear witness to the current activity in the field. This prompt us to disclose the full experimental details associated with the preliminary communicated synthesis of topsentins[4c] along with new related approaches and results comprising the effect induced by changing the protecting groups.

2. Results and discussion

When the two approaches depicted in Scheme 1 were applied to the synthesis of deoxytopsentin **1** that following route a_1 proved more efficient and led to **1** in higher overall yield. Indeed, compound **1** was synthesized through route a_1 in 50% yield from the (indolyl)aldehyde **7a**, whereas route a_2 provided the target compound in a satisfactory, but considerably lower, 30% yield from the (imidazolyl)aldehyde **8c** (Scheme 2). The secondary alcohol **9** was the common product for the first step in each variant. In route a_1 alcohol **9** was formed in 84% isolated yield from the attack of the *N*-protected 2-lithioimidazole **8b** on the *N*-protected indole-3-carboxaldehyde **7a** in THF at low temperature. Aldehyde **7a** was readily prepared in high yield from commercially available indole-3-carboxaldehyde according to a known protocol[8] and the organolithium reagent **8b** was generated in situ as described in the literature,[9] by the action of *n*-butyllithium on the 4,5-diiodo-*N*-protected imidazole derivative **8a** at −78 °C for 45 min. The



Scheme 2. Synthesis of deoxytopsentin **1** and topsentin **2**.

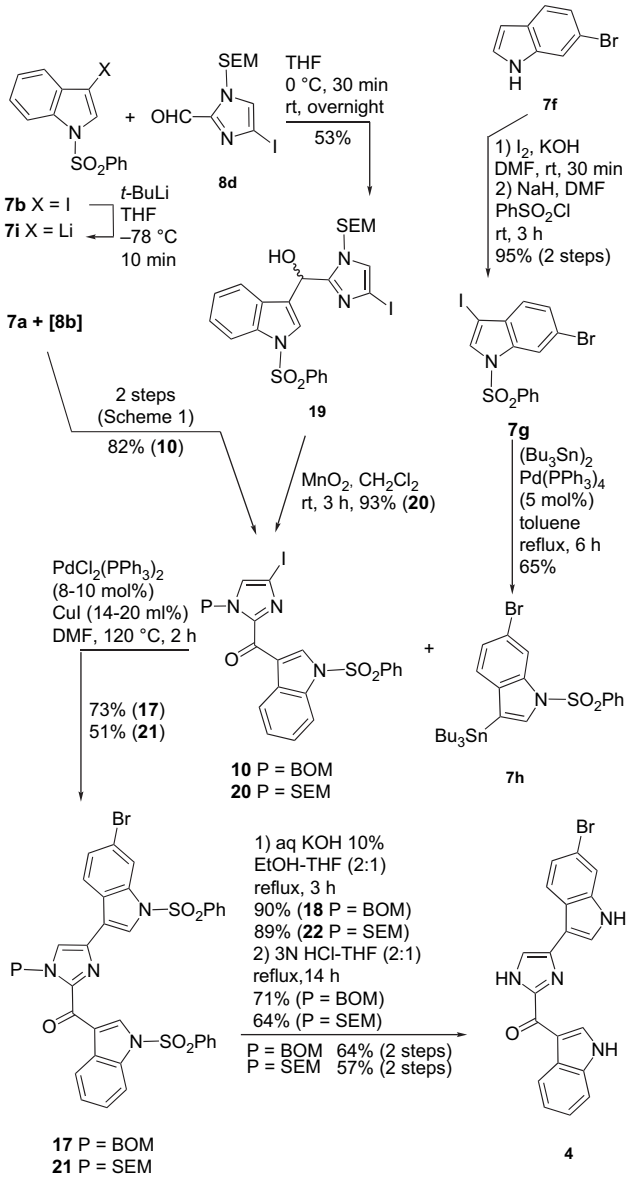
reaction time before addition of compound **7a** must be strictly controlled since it was shown[9] that the 2-imidazolyllithium derivative **8b** is formed via acid/base equilibration of the 4-imidazolyllithium derivative (not shown in Scheme 2) initially produced. The benzyloxymethyl (BOM) group plays a major role directing, regiospecifically, the initial metal–halogen exchange to the vicinal position through chelation of the oxygen atom to the 5-lithio substituent. By the alternative route a_2 alcohol **9** was isolated in 50% yield from the reaction of imidazole-2-carboxaldehyde **8c** with 3-indolyl-magnesium bromide **7c**. The Grignard reagent was generated in situ, as already described,[10] by halogen–magnesium exchange of 3-iodoindole **7a**[11] with ethylmagnesium bromide. Aldehyde **8c** was easily prepared following a described procedure from protected diiodoimidazole **8a**, by quenching the organolithium derivative **8b** with dimethylformamide.[9] The oxidation of the secondary alcohol **9** with excess manganese dioxide at rt led to the corresponding carbonyl derivative **10** in high yield thus achieving the formation of the desired aryl–carbonyl bond. The formation of **10** from **9** was characterized by the disappearance of the signals of the CH and OH protons of the alcohol in the ^{1}H NMR spectrum, at 6.2 ppm (br d, 1H, J=5.5 Hz) and 5.85 ppm (br d, 1H, J=5.5 Hz), respectively, and also in the ^{13}C NMR spectrum by the appearance of the signal of the carbonyl carbon of **10** at 177.2 ppm with the concomitant disappearance of the signal of the carbon bearing the OH of **9** at 63.8 ppm. The oxidation yield was obviously independent of the way in which the alcohol was prepared. Therefore, on account of the results for the arylation step, the formation of a 2-imidazolyl–carbonyl bond should be preferred over the formation of 3-indolyl–carbonyl bond so as to achieve improved yield.

The remaining 4-imidazolyl–3-indolyl bond, needed to complete the assembly of the deoxytopsentin core, was built through palladium-catalyzed cross-coupling between the iodo-imidazole moiety of **10** and 3-stannylindole **7d**, which was readily prepared from 3-iodoindole **7b** as described.[12] This reaction, performed in DMF at 120 °C for 2 h and using copper iodide as co-catalyst,[13] led to the fully protected deoxytopsentin derivative **11** in 76% yield from **10**, thus amounting a 63% overall yield from indole **7a** according to route a_1, or a 37% overall yield from imidazole **8c** according to route a_2.

The *N*-protecting groups were smoothly removed in two steps using standard conditions. Thus alkaline hydrolysis of **11** under reflux, with ethanol and THF as co-solvents, deprotected the indolyl moieties leading to intermediate **12** (*N*-BOM-imidazolyl derivative not shown in Scheme 2) in 86% yield. Finally, the benzyloxymethyl group was conveniently removed using ammonium formate as the hydrogen donor and palladium on carbon as catalyst[14] furnishing the expected deoxytopsentin **1** in 96% yield from **12** (overall deprotection yield of 82%). Spectroscopic data for compound **1** were in agreement with those described for natural deoxytopsentin.[1b]

Route a_1 was also applied to the synthesis of topsentin **2**, which was obtained in 47% yield from the known indole-3-carboxaldehyde **7e**[15] as summarized in Scheme 2. The arylation of aldehyde **7e** by the organolithium reagent **8b** followed by oxidation of the corresponding secondary alcohol **13** led to the 2-indolylcarbonyl-4-iodoimidazole **14** in 64% yield from **7e**. Subsequent Stille cross-coupling with stannane **7d** produced topsentin derivative **15** in 79% isolated yield from **14**. This three-step sequence, carried out under the conditions already described for the synthesis of **1**, afforded protected topsentin **15** in 51% overall yield. Deprotection leading to topsentin **2** was also performed as before, in two steps, since the benzyl ether protection for the OH group was selected as to allow smooth cleavage of the benzylether[14] together with the imidazole *N*-BOM group. Thus alkaline treatment of **15** under reflux for 3 h led to the desulfonylated derivative, *N*-benzyloxymethyl-*O*-benzyl topsentin **16** (not shown in Scheme 2) and subsequent hydrogenolysis afforded free topsentin **2** in 92% yield from **15**. Spectroscopic data for compound **2** were in agreement with those previously described for natural topsentin.[1b] The formation of the cross-coupling product **15** from compound **14** can be monitored by the disappearance of the signal of the carbon bearing the halogen of **14**, at 83.1 ppm in the ^{13}C NMR spectrum, and the downfield shift of the proton in position-2 of the indolyl residue in the ^{1}H NMR spectrum, from δ 9.1 ppm (s, 1H) in the substrate **14** to δ 9.6 ppm (s, 1H) in the product **15**. A similar deprotection for the signal of the proton in position 2 of the indolyl moiety (which resonated at 9.27 ppm (s) in **10** and 9.6 ppm (s) in **11**) was associated with the coupling of the iodoketone **10** with stannane **7d** leading to the protected deoxytopsentin derivative **11**. Full deprotection furnishing the target **2** was characterized by the splitting of the signals in the ^{1}H and ^{13}C NMR spectra in neutral solution because of the formation of two isomers. As described,[1a,b] upon addition of a strong acid to the NMR solvent, both tautomers are protonated leading to the same salt thus suppressing the splitting of the NMR signals. These spectral features and trends as well as those already pointed out for the transformation of **9** to **10** by alcohol oxidation hold in all cases we examined. Therefore, they are valuable tools for monitoring the progress of the entire process.

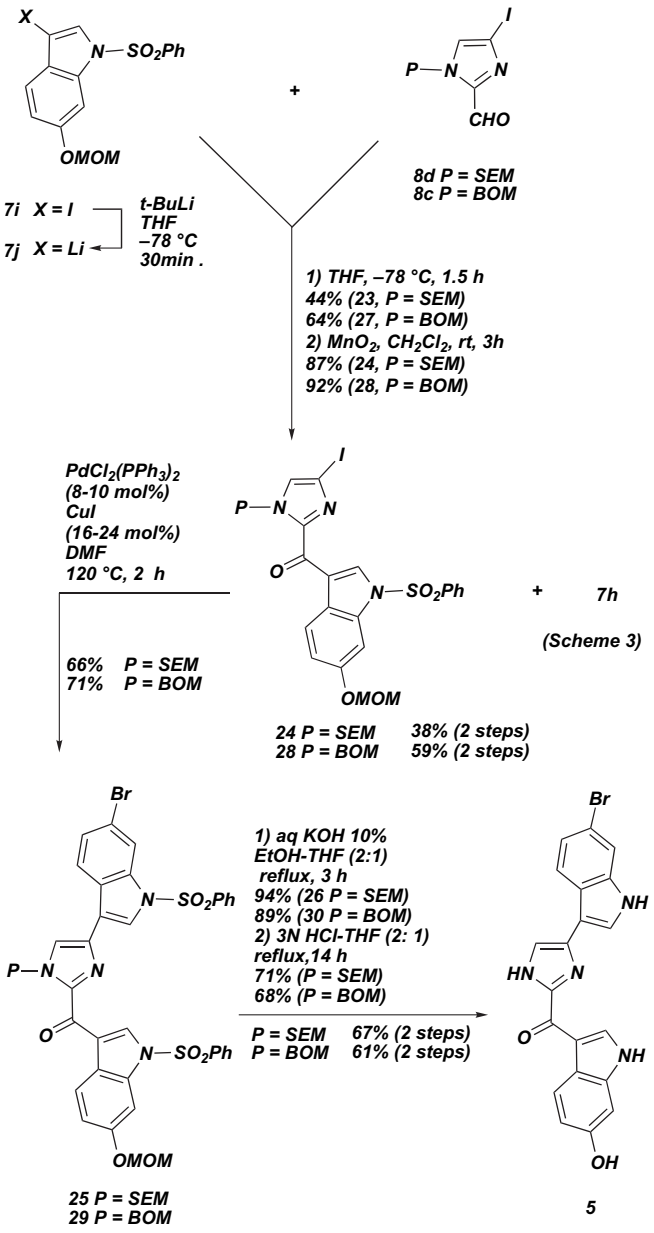
The synthesis of bromodeoxytopsentin **4** through pathways a_1 and a_2 is detailed in Scheme 3. Once again the first one (path a_1)



Scheme 3. Synthesis of bromodeoxytopsentin **4**.

provided the target **4** in higher overall yield (39% from aldehyde **7a**) than the second (15% from aldehyde **8d**). With regard to path a_1, the 5-iodoimidazole derivative **10** already prepared (Scheme 2) was an intermediate for the projected cross-coupling with bromoindolyl stannane **7h** en route to compound **17**. The organostannane **7h** was obtained in 65% yield by palladium-catalyzed coupling of the protected 3-iodo-6-bromoindole **7g** with hexabutylditin using a set of reaction conditions already described in the literature for the synthesis of other closely related indolylstannyl derivatives.[16] The starting iodide **7g** could be conveniently prepared in high yield from the commercially available 6-bromoindole **7f** as shown in Scheme 3, via the parent 3-iodo-6-bromoindole and subsequent N-phenylsulfonylation of that intermediate. The Stille reaction of **10** with **7h**, performed under the previously described conditions, afforded the fully protected derivative **17** in 73% yield from **10**. The overall yield of the three-step sequence leading to **17** from indole-3-carboxaldehyde **7a** was thus 60%, the same figure as for the transformation **7a** to **11** (Scheme 2). These results underline the synthetic utility of our approach, which allow an access to all members of the topsentin family, including the brominated ones, through a single set of standard reaction conditions. The key feature is that the Stille coupling is iodide specific and tolerates an aryl bromide. Thus, stannane **7h** is an efficient reagent for the cross-coupling step as the bromoaryl moiety is not affected. Needless to say, besides the syntheses of bromotopsentins herein described (Schemes 3 and 4), access to stannane **7h** opened a way for its use in the synthesis of other natural products containing the 6-bromoindolyl moiety.[17] Although, the cross-coupling reactions of the iodoimidazole **10** with the brominated stannylindole **7h** (Scheme 3) or with the unsubstituted indolylstannylindole **7d** (Scheme 2) could be performed under the same conditions, the deprotection protocol for compound **17** had to be modified since the use of hydrogenolytic conditions should most probably result in concomitant dehalogenation.[1b,18] As a consequence, after the initial alkaline hydrolysis of compound **17** leading to the corresponding desulfonylated *N*-BOM derivative **18** (not shown in Scheme 3) we took advantage of the lability of the benzyloxymethyl group under mildly acidic conditions.[9,19] Thus the remaining BOM protecting group was removed without affecting the bromoindole moiety through acid hydrolysis, by refluxing compound **18** in a 3 N HCl/THF mixture. The deprotection sequence afforded bromodeoxytopsentin **4** in 64% overall yield from the entirely protected precursor **17**. Spectroscopic data for compound **4** were in agreement with those described for natural bromodeoxytopsentin.[1f]

Another protecting group was tested in path a_2, which started by the arylation of the (imidazolyl)aldehyde **8d**. We though that it was wise to use the [2-(trimethylsilyl)ethoxy]methyl (SEM) protecting group for imidazole as this moiety may be easily removed under acidic conditions.[20] Moreover, as an *ortho*-directing group it is well suited to induce a regiospecific metalation leading to **8d** from the parent 4,5-diiodoimidazolyl derivative. In this way, it should behave similarly to the BOM moiety in the transformation of **8a** into **8c** (see Scheme 2). Thus, addition of the 3-lithioindole reagent **7f** to aldehyde **8e** led to the secondary alcohol **19** in 53% yield. As we also observed an equivalent yield for the closely related addition of the (indolyl)Grignard **7c** to aldehyde **8c** leading to alcohol **9** (Scheme 2) it follows that the nature of the indolyl-organometallic reagent plays a minor role in the outcome of these reactions. Subsequent MnO_2 oxidation of **19** in high yield and cross-coupling of the corresponding carbonyl derivative **20** with stannylindole **7h** in 51% yield led to the fully protected compound **21** in 25% overall yield from **8d**. Deprotection of compound **21** using the two-step sequence previously described for the closely related BOM derivative **17** led to bromodeoxytopsentin **4** in 57% overall yield. Thus both the BOM and SEM moieties used in pathways a_1 and a_2 proved satisfactory for the final two-step deprotection.



Scheme 4. Synthesis of bromotopsentin **5**.

Indeed, they avoided dehalogenation and displayed similar overall efficiency. Nevertheless, BOM appeared as superior to SEM for the Stille reaction with stannane **7h**. The cross-coupling compound **17** was produced from iodoimidazole **10** in considerably higher yield than the SEM-protected compound **21** from iodoimidazole **20**.

The efficiency of these protecting groups was also evaluated in the synthesis of bromotopsentin **5** through pathway a_2 (Scheme 4). With stannane **7h** in hand, the 2-indolylcarbonyl-4-iodoimidazole derivatives (**24** and **28**) needed as counterparts for the projected cross-coupling leading to fully protected bromotopsentins (**25** and **29**) were prepared. Thus, compound **25** was obtained by the organolithium-mediated addition of the (*N*,*O*-bisprotected)-6-hydroxy-3-iodoimidazole **7i** to the imidazolylaldehyde **8e** and compound **26** was prepared by a similar organolithium addition to aldehyde **8c**.[4b] The iodoindole **7i** was prepared from 4-OMOM-benzaldehyde. The corresponding ethyl 2-indolylcarboxylate was prepared according to Moody[22] and then saponified. Subsequent decarboxylation afforded 6-(methoxymethoxy)-1*H*-indole that was iodinated and protected, by N-phenylsufonation, following

standard procedures. For the O-protection of the starting organolithium reagent **7j** the methoxymethyl (MOM) group was preferred to the benzyl group used in the synthesis of topsentin **2** (Scheme 2). The MOM moiety may be removed under acidic treatment,[21] and thus concomitantly with the imidazole protecting groups (SEM or BOM). Hence, an alkaline–acidic deprotection sequence, similar to that previously used (Scheme 3), afforded free bromotopsentin **5** from the *N*,*O*-protected precursors **25** and **29** without reductive debromination. Spectroscopic data for the corresponding compound **5** were in agreement with those described for natural bromotopsentin.[1b] Once more, BOM protection for the imidazolyl moiety of the starting aldehyde afforded improved overall yield of the target **5** (25% from aldehyde **8c** vs 15% from aldehyde **8e**), although the decisive step that confirms the preference for BOM over SEM was here the first one, leading to the corresponding secondary alcohols, instead of the cross-coupling step as before (Scheme 3). Indeed, whereas the arylation of the SEM-protected substrate **8d** led to the indolyl-imidazolyl carbinol **23** in 44% yield, under identical conditions alcohol **27** was obtained in 64% yield from aldehyde **8c** displaying *N*-BOM protection for the imidazole ring. All subsequent steps, from alcohol oxidation to the final acidic deprotection showed very close yields for the corresponding reactions involving the SEM or the BOM moieties as *N*-protecting groups for the imidazole residue. The silylated moiety showed enhanced lability throughout organometallic reactions (Schemes 3 and 4) as well as throughout workup and purification processes. All of that may account for the lower overall yields often encountered with *N*-SEM-protected imidazole derivatives involved therein. But in any case and as a matter of facts, the BOM protecting group proved superior to the SEM in the sequences leading to topsentins following routes a_1 and a_2. It is also more versatile allowing convenient removal either under neutral or acidic conditions and thus may be widely used.

3. Conclusion

In summary, we developed effective procedures for the synthesis of several bioactive marine bis-indole alkaloids belonging to the topsentin family using commercially available and inexpensive starting materials. Our strategy is simple and compares favorably with other procedures. It calls for an aldehyde-arylation/alcohol-oxidation sequence leading to 2-(3-indolyl)carbonyl-5-iodoimidazole derivatives followed by the transition metal-catalyzed heteroarylation of those intermediates with the appropriate 3-stannylindole. The syntheses may be started either with a 3-indolylcarboxaldehyde or 2-imidazolyl-carboxaldehyde as the substrate. Experimental evidence suggested that arylation of 3-indolyl-aldehydes by 2-imidazolyl-organometallic reagents in the first step is the most convenient pathway when both starting materials are available. This methodology offers, we believe, a valuable alternative for a general access to topsentin derivatives and moreover its scope should be easily extended for the synthesis of other bis-indolyl alkaloids and related analogs.

4. Experimental section

4.1. General information

NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts (δ) are given in parts per million relative to TMS or to the solvent signal and coupling constants (J) are given in hertz. Mass spectra and HRMS were obtained using EI as ion sources. IR spectra were recorded as KBr pellets or neat. Elemental analyses were performed at the microanalytical laboratory of ICSN-CNRS. Melting points were not corrected. UV spectra were recorded in EtOH solution. Commercially available compounds were used as received, without further purification. When needed, solvents were distilled and dried by standard methods. THF was distilled from benzophenone ketyl; CH_2Cl_2 and toluene were distilled from CaH_2. All reactions were monitored by TLC using commercial silica gel plates and visualization was accomplished by UV light and by staining with PMA solution (5 g of phosphomolybdic acid in 100 mL of EtOH) and heating. Flash chromatography was performed on silica gel 60 Å (1% NEt_3 in the mobile phase was used to deactivate the solid phase when needed).

4.2. Synthesis of deoxytopsentin 1

(1-Benzenesulfonyl-1H-indol-3-yl)-(1-benzyloxymethyl-4-iodo-1H-imidazol-2-yl)-methanol ***9***. (a) By addition of 2-Li-imidazole **8b** to 1-benzenesulfonyl-1*H*-indole-3-carboxaldehyde **7a**: to a solution of compound **8a** (886 mg, 2 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (1.6 M, 1.5 mL) and the reaction mixture was stirred for 45 min at that temperature. To the solution of the corresponding imidazol-2-yllithium derivative **8b**[9] thus formed was added dropwise a solution of aldehyde **7a** (298 mg, 1.04 mmol) in THF (6 mL) and then the reaction mixture was slowly warmed to 5 °C (over 4 h). It was then diluted with CH_2Cl_2, washed (saturated NH_4Cl and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 92:8) provided the secondary alcohol **9** (529 mg, 85%) as a white solid; mp 163–164 °C. R_f 0.42 (CH_2Cl_2/EtOAc 9:1); IR (KBr, ν cm^{-1}) 3275–3037, 1448, 1375, 1182, 1080; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H, J=8.2 Hz), 7.85 (br d, 2H, J=7.9 Hz), 7.7 (br s, 1H), 7.42 (m, 1H), 7.38–7.16 (m, 8H), 7.11 (m, 1H), 7.04–6.95 (m, 2H), 6.98 (s, 1H), 6.2 (br d, 1H, J=5.5 Hz), 5.85 (br d, 1H, J=5.5 Hz, exchangeable with D_2O), 5.2 (d, 1H, J_{AB}=10.1 Hz), 5.07 (d, 1H, J_{AB}=10.1 Hz), 4.07 (d, 1H, J_{AB}=12.4 Hz), 3.94 (d, 1H, J_{AB}=12.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4, 137.9, 135.9, 135.5, 133.9, 129.2, 128.5, 128.2, 128.1, 127.5, 126.7, 125.1, 123.6, 122.4, 120.2, 113.6, 79.7, 74.6, 70.5, 63.8; HRMS m/z 599.0381 calcd for $C_{26}H_{22}N_3O_4SI$; found 599.0375. Anal. Calcd for $C_{26}H_{22}IN_3O_4S$: C, 52.09; H, 3.77; N, 7.01. Found: C, 52.18; H, 3.71; N, 6.89. (b) By addition of indole-Grignard **7c** to aldehyde **8c**: (b1) preparation of *1-benzyloxymethyl-4-iodo-1H-imidazole-2-carboxaldehyde* ***8c***: to a solution of imidazole (4 g, 58.8 mmol) in 2 M NaOH (360 mL) was slowly added a solution of I_2 (28 g, 110 mmol) and KI (35 g, 105 mmol) in H_2O (180 mL). The mixture was stirred overnight at rt and then neutralized (with AcOH). The precipitate was filtered. The solid was washed with H_2O and air-dried to furnish 4,5-diiodoimidazole[23] (16.1 g, 85%) as a white powder. To a solution of the latter (6 g, 18.6 mmol) in DMF (50 mL) at rt was added K_2CO_3 (26 g, 188 mmol) and then benzyloxymethylchloride BOMCl (4 mL, 28 mmol). The reaction mixture was stirred at rt overnight, then filtered and the filtrate was evaporated under vacuum. Flash chromatography (CH_2Cl_2) of the oily residue led to 1-benzyloxymethyl-4,5-diiodo-1*H*-imidazole **8a**[9] (5.1 g, 62%). To a solution of compound **8a** (1.2 g, 2.7 mmol) in THF (25 mL) at −78 °C was added *n*-BuLi (1.6 M, 2 mL) and the solution was stirred at that temperature for 45 min. It was then quenched by addition of dry DMF (1.5 mL) and stirred for a further 10 min. Then the mixture was slowly warmed to rt and then treated with a saturated aqueous solution of NH_4Cl and EtOAc. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with hexane/EtOAc 3:1) furnished the aldehyde **8c**[9] (675 mg, 72%) as an essentially white solid. (b2) To a solution of 3-iodoindole **7b**[11] (200 mg, 0.52 mmol) in dry THF (4 mL) at 0 °C was added a diethyl ether solution of EtMgBr (3 M, 0.21 mL) at 0 °C and then the reaction mixture was allowed to warm to rt and stirred for 30 min. To the resulting Grignard derivative **7c**[10] was added a solution of aldehyde **8c** (178 mg, 0.52 mmol) in THF (2 mL). The reaction mixture was allowed to warm to rt and then stirred

overnight. It was then diluted with CH_2Cl_2 and washed (saturated NH_4Cl and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 92:8) led to the alcohol **9** (155 mg, 50%) as a white solid. *(1-Benzenesulfonyl-1H-indol-3-yl)-(1-benzyloxymethyl-4-iodo-1H-imidazol-2-yl)-methanone* ***10***. To a solution of the secondary alcohol **9** (380 mg, 0.63 mmol) in CH_2Cl_2 (20 mL) was added MnO_2 (1.4 g) and the resulting suspension was stirred for 3 h at rt. The reaction mixture was filtered (rinsing with CH_2Cl_2) and the filtrate was evaporated leading to compound **10** (370 mg, 98%) as an oil, which solidified on standing in the refrigerator. R_f 0.67 (CH_2Cl_2); IR (KBr, ν cm^{-1}) 3151, 3128, 2876, 1630, 1529, 1450, 1377, 1192, 1178, 1080, 979; ^1H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.43 (m, 1H), 8.05–7.95 (m, 3H), 7.57 (m, 1H), 7.49 (m, 2H), 7.41 (s, 1H), 7.39–7.25 (m, 7H), 5.92 (s, 2H), 4.61 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 144.6, 137.6, 136.3, 134.43, 134.37, 129.5, 128.5, 128.3, 128.2, 127.8, 127.2, 125.6, 124.8, 122.9, 118.7, 113.1, 83.1, 76.7, 71.7; HRMS *m*/*z* 597.0221 calcd for $C_{26}H_{20}IN_3O_4S$; found 597.0219. Anal. Calcd for $C_{26}H_{20}IN_3O_4S$: C, 52.27; H, 3.37; N, 7.03. Found: C, 52.19; H, 3.53; N, 6.78. *1-Benzenesulfonyl-3-tributylstannyl-1H-indole* ***7d***. To a solution of 3-iodoindole **7b** (1 g, 2.6 mmol) in toluene (25 mL) was added hexabutylditin (1.6 mL, 3.17 mmol) and $Pd(PPh_3)_4$ (150 mg, 0.13 mmol). The reaction mixture was refluxed for 6 h under argon, cooled to rt, and evaporated to dryness affording an oily residue (3.05 g), which was purified by column chromatography (eluting with hexane/Et_2O/Et_3N 94:5:1) to give stannane **7d**[12] (927 mg, 65%). *(1-Benzenesulfonyl-1H-indol-3-yl)-[4-(1-benzenesulfonyl-1H-indol-3-yl)-1-benzyloxymethyl-1H-imidazol-2-yl]-methanone* ***11***. To a solution of compound **10** (230 mg, 0.38 mmol) in DMF (5 mL) under argon was added $Pd(PPh_3)_2Cl_2$ (30 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), and a solution of the stannane **7d** (280 mg, 0.51 mmol) in DMF (3 mL). The reaction mixture was warmed at 120 °C under argon and stirred at the same temperature for 2 h. Then the reaction mixture was cooled to rt, diluted with CH_2Cl_2, washed (15% ammonia and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/hexane 4:1) gave compound **11** (211 mg, 75%) as a colored thick syrup. R_f 0.33 (CH_2Cl_2/hexane 4:1); IR (KBr, ν cm^{-1}) 3159, 3065, 2928, 1635, 1533, 1446, 1375, 1184, 1132, 1097, 976; ^1H NMR (300 MHz, $CDCl_3$) δ 9.6 (s, 1H), 8.47 (dd, 1H, *J*=8.3, 2.3 Hz), 8.27 (d, 1H, *J*=7.3 Hz), 8.09 (d, 1H, *J*=8 Hz), 8.02 (d, 2H, *J*=8.2 Hz), 8.0 (s, 1H), 7.94 (d, 2H, *J*=7.3 Hz), 7.62 (s, 1H), 7.56–7.15 (m, 16H), 6.02 (s, 2H), 4.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 142.5, 137.9, 137.6, 136.6, 135.4, 134.5, 134.4, 133.9, 129.6, 129.3, 128.6, 128.5, 128.1, 127.8, 127.1, 126.8, 125.6, 125.2, 124.8, 123.9, 122.9, 122.7, 121.5, 120.8, 119.0, 116.4, 113.7, 113.0, 76.9, 71.5; HRMS *m*/*z* 726.1658 calcd for $C_{40}H_{30}N_4O_6S_2$; found 726.1606. Anal. Calcd for $C_{40}H_{30}N_4O_6S_2$: C, 66.10; H, 4.16; N, 7.71. Found: C, 65.88; H, 4.29; N, 7.42. *[1-Benzyloxymethyl-4-(1H-indol-3-yl)-1H-imidazol-2-yl]-(1H-indol-3-yl)-methanone* ***12***. To a solution of compound **11** (180 mg, 0.248 mmol) in EtOH/THF (15 mL:4 mL) was added a 10% aqueous KOH solution (5 mL). The reaction mixture was stirred at reflux temperature for 2 h and then cooled to rt and concentrated under vacuum. The residue was diluted with EtOAc, washed (H_2O and brine), dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2:EtOAc 9:1) furnished compound **12** (95 mg, 86%) as a pale yellow powder; mp 173–175 °C; R_f 0.4 (CH_2Cl_2:EtOAc 9:1); IR (KBr, ν cm^{-1}) 3402–3343, 1605, 1521, 1468, 1375, 1431, 1076; ^1H NMR (300 MHz, DMSO-d_6) δ 12.2 (br s, 1H), 11.4 (br s, 1H), 9.22 (d, 1H, *J*=3.0 Hz), 8.5 (br dd, 1H, *J*=5.9, 3.2 Hz), 8.2 (br d, 1H, *J*=7.2 Hz), 8.05 (s, 1H), 7.95 (d, 1H, *J*=2.4 Hz), 7.62 (br dd, 1H, *J*=5.9, 3.2 Hz), 7.53 (br d, 1H, *J*=7.3 Hz), 7.40–7.15 (m, 9H), 6.08 (s, 2H), 4.7 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.0, 142.8, 137.8, 137.7, 137.0, 136.8, 136.5, 128.4, 127.8, 127.0, 125.1, 123.3, 123.2, 122.3, 121.9, 121.7, 120.2, 119.8, 119.6, 115.1, 112.5, 112.0, 109.6, 76.6, 70.6; HRMS *m*/*z* 446.1716 calcd for $C_{28}H_{22}N_4O_2$; found 446.1742. Anal. Calcd for $C_{28}H_{22}N_4O_2$ 1/2H_2O: C, 73.83; H, 5.09; N, 12.30. Found: C, 73.78; H, 5.06; N, 12.33. *Deoxytopsentin* ***1***. A solution of compound **12** (90 mg, 0.2 mmol) in EtOH (15 mL) containing 10% Pd/C (40 mg) and ammonium formate[14] (170 mg, 2.6 mmol) was refluxed for 3 h. The reaction mixture was then cooled to rt and filtered through a pad of Celite (rinsing with CH_2Cl_2 and EtOAc). The filtrate was evaporated under reduced pressure to provide deoxytopsentin **1** (63 mg, 96%) as a yellow solid; R_f 0.36 (CH_2Cl_2:MeOH 19:1); IR (KBr, ν cm^{-1}) 3366–3283, 2926, 1582, 1527, 1458, 1429, 1238, 1105; UV (EtOH, λ_{max} nm) 208, 230, 253, 273, 375; ^1H NMR (300 MHz, 1% TFA in DMSO-d_6) δ 12.38 (br s, 1H), 11.56 (br s, 1H), 9.05 (d, 1H, *J*=2.5 Hz), 8.38 (m, 1H), 8.08 (br d, 1H, *J*=2.7 Hz), 8.04 (br d, 1H, *J*=7.6 Hz), 7.91 (s, 1H), 7.60 (m, 1H), 7.51 (br d, 1H, *J*=7.4 Hz), 7.30 (m, 2H), 7.26–7.15 (m, 4H); ^{13}C NMR (75 MHz, 1% TFA in DMSO-d_6) δ 175.2, 144.3, 137.7, 136.8, 136.7, 133.7, 126.6, 124.9, 124.5, 123.6, 122.5, 122.1, 121.9, 120.2, 120.0, 119.8, 119.7, 114.0, 112.8, 112.3, 106.2; HRMS *m*/*z* 326.1167 calcd for $C_{20}H_{14}N_4O$; found 326.1169.

4.3. Synthesis of topsentin 2

1-Benzenesulfonyl-6-benzyloxy-1H-indole-3-carboxaldehyde ***7e***. A solution of 6-benzyloxy-1*H*-indole-3-carboxaldehyde[15] (680 mg, 2.7 mmol) in DMF (8 mL) was slowly added to a suspension of NaH (60%, 150 mg, 3.7 mmol) in THF (25 mL) at 0 °C. The reaction mixture was stirred for 30 min and $PhSO_2Cl$ (0.5 mL, 3.3 mmol) was added. After that, the cooling bath was removed and the reaction mixture was stirred overnight at rt. It was then diluted with CH_2Cl_2, washed (saturated $NaHCO_3$ and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by flash chromatography (eluting with CH_2Cl_2/hexane 9:1) led to aldehyde **7e** (985 mg, 93%) as a white solid. R_f 0.51 (CH_2Cl_2/hexane 9:1); IR (KBr, ν cm^{-1}) 3134–3070, 2824, 2739, 1682, 1217–1186, 738, 729; ^1H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.1 (d, 1H, *J*=8.2 Hz), 8.09 (s, 1H), 7.78 (d, 2H, *J*=8.2 Hz), 7.6–7.3 (m, 9H), 7.06 (dd, 1H, *J*=8.2, 2.0 Hz), 5.1 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 157.9, 137.3, 136.7, 136.3, 135.1, 134.6, 129.6, 129.2, 128.7, 128.0, 127.3, 127.0, 123.2, 122.7, 120.0, 115.0, 98.7, 70.5; MS *m*/*z* 391 (M^+, 70%), 300 (M^+−Bn, 10%). *(1-Benzenesulfonyl-6-benzyloxy-1H-indol-3-yl)-(1-benzyloxymethyl-4-iodo-1H-imidazol-2-yl)-methanol* **13**. To a solution of compound **8a** (1 g, 2.27 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (1.6 M, 1.6 mL) and the reaction mixture was stirred for 45 min at that temperature. Then, to the resulting solution of the imidazol-2-yllithium derivative **8b** was added a solution of aldehyde **7e** (300 mg, 0.77 mmol) in THF (5 mL) and the reaction mixture was slowly warmed to 0 °C. It was then treated with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 9:1) provided the alcohol **13** (400 mg, 74%) as a thick syrup, which solidified upon cooling; mp 145–146 °C. R_f 0.22 (CH_2Cl_2/EtOAc 9:1); IR (KBr, ν cm^{-1}) 3144–3040, 1618, 1489, 1209, 1174, 1105; ^1H NMR (300 MHz, $CDCl_3$) δ 7.7 (br d, 2H, *J*=7.4 Hz), 7.55 (d, 1H, *J*=2.15 Hz), 7.5–7.2 (m, 13H), 7.15 (d, 1H, *J*=8.7 Hz), 7.1 (br dd, 2H, *J*=7.3, 3.5 Hz), 7.01 (s, 1H), 6.85 (dd, 1H, *J*=8.7, 2.3 Hz), 5.13 (s, 2H), 5.10 (d, 1H, *J*=10.7 Hz), 4.97 (d, 1H, *J*=10.7 Hz), 4.18 (d, 1H, *J*=11.8 Hz), 4.07 (d, 1H, *J*=11.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 150.4, 137.9, 136.8, 136.4, 136.0, 133.7, 129.1, 128.6, 128.4, 128.0, 127.9, 127.5, 127.3, 126.6, 126.3, 122.53, 122.46, 122.1, 120.8, 113.5, 99.2, 79.6, 74.6, 70.4, 70.3, 63.8; HRMS *m*/*z* 705.0768 calcd for $C_{33}H_{28}IN_3O_5S$; found 705.0794. *(1-Benzenesulfonyl-6-benzyloxy-1H-indol-3-yl)-(1-benzyloxymethyl-4-iodo-1H-imidazol-2-yl)-methanone* ***14***. To a solution of secondary alcohol **13** (600 mg, 0.85 mmol) in CH_2Cl_2 (70 mL) was added MnO_2 (1.7 g, 19.5 mmol). The reaction mixture was stirred at rt for 3 h and then filtered. The

solid residue was rinsed (CH_2Cl_2, Et_2O). The filtrate was evaporated under reduced pressure to provide ketone **14** (520 mg, 87%) as a colored syrup. An analytical sample was prepared by filtering on silica gel. R_f 0.83 (CH_2Cl_2/EtOAc 9:1); IR (KBr, ν cm^{-1}): 3144–3040, 1618, 1489, 1209, 1174, 1105; ^1H NMR (300 MHz, $CDCl_3$) δ 9.1 (s, 1H), 8.36 (d, 1H, J=8.9 Hz), 7.85 (d, 1H, J=8.8 Hz), 7.83 (s, 1H), 7.56 (d, 1H, J=2.2 Hz), 7.54–7.35 (m, 9H), 7.3–7.2 (m, 5H), 7.1 (dd, 1H, J=8.9, 2.4 Hz), 5.89 (s, 2H), 5.17 (s, 2H), 4.59 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 157.4, 144.6, 137.5, 136.8, 136.3, 135.3, 134.3, 129.5, 128.6, 128.5, 128.2, 128.0, 127.7, 127.3, 127.1, 123.5, 122.3, 118.9, 114.6, 98.7, 83.1, 76.8, 71.6, 70.4; HRMS m/z 703.0675 calcd for $C_{33}H_{26}IN_3O_5S$; found 703.0638. *(1-Benzenesulfonyl-6-benzyloxy-1H-indol-3-yl)-[4-(1-benzenesulfonyl-1H-indol-3-yl)-1-benzyloxymethyl-1H-imidazol-2-yl]-methanone* ***15***. To a solution of compound **14** (400 mg, 0.57 mmol) in DMF (10 mL), under argon, were successively added $Pd(PPh_3)_2Cl_2$ (32 mg, 0.011 mmol), CuI (20 mg, 0.1 mmol), and then a solution of the stannane **7d** (280 mg, 0.51 mmol) in DMF (3 mL). The reaction mixture was heated and stirred under argon at 120 °C for 2 h. After cooling to rt, the reaction mixture was concentrated, taken up in CH_2Cl_2, filtered through Celite, washed (15% NH_4OH and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/hexane 4:1) afforded compound **15** (375 mg, 79%) as a yellow fluffy solid. R_f 0.44 (CH_2Cl_2/hexane 4:1); IR (KBr, ν cm^{-1}) 3151–3067, 2924, 1628, 1531, 1448, 1375, 1182, 1093; ^1H NMR (300 MHz, $CDCl_3$) δ 9.4 (s, 1H), 8.31 (d, 1H, J=8.8 Hz), 8.24 (d, 1H, J=8.2 Hz), 8.07 (d, 1H, J=8.6 Hz), 7.98 (s, 1H), 7.95 (d, 2H, J=7.4 Hz), 7.88 (d, 2H, J=7.8 Hz), 7.62 (s, 1H), 7.6–7.2 (m, 19H), 7.07 (dd, 1H, J=2.0, 8.7 Hz), 5.99 (s, 2H), 5.18 (s, 2H), 4.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 157.4, 142.5, 138.0, 137.7, 136.8, 136.6, 135.5, 135.4, 134.3, 133.9, 129.6, 129.3, 128.6, 128.5, 128.1, 120.0, 127.8, 127.4, 127.0, 126.8, 125.2, 123.9, 123.5, 122.7, 122.4, 121.5, 120.7, 119.2, 116.5, 114.5, 113.7, 98.6, 76.9, 71.5, 70.4; HRMS m/z 832.2035 calcd for $C_{47}H_{36}N_4O_7S_2$; found 832.2025. Anal. Calcd for $C_{47}H_{36}N_4O_7S_2\cdot 1/4H_2O$: C, 67.41; H, 4.39; N, 6.69. Found: C, 67.29; H, 4.45; N, 6.56. *(6-Benzyloxy-1H-indol-3-yl)-[1-benzyloxymethyl-4-(1H-indol-3-yl)-1H-imidazol-2-yl]-methanone* ***16***. To a solution of compound **15** (330 mg, 0.396 mmol) in EtOH/THF (4:1, 25 mL) was added a 10% aqueous KOH solution (10 mL). The reaction mixture was stirred under reflux for 2 h, then cooled to rt and concentrated under vacuum. The residue was diluted with EtOAc. The organic layer was washed (H_2O, brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 9:1) afforded compound **16** (212 mg, 97%) as a yellow solid. R_f 0.41 (CH_2Cl_2/EtOAc 9:1); IR (KBr, ν cm^{-1}) 3397, 1608, 1506, 1452, 1080, 874; ^1H NMR (300 MHz, $CDCl_3$) δ 10.1 (br s, 1H), 8.57 (d, 1H, J=3 Hz), 8.41 (d, 1H, J=8.7 Hz), 8.04 (br s, 1H), 7.8 (d, 1H, J=7.5 Hz), 7.49 (s, 1H), 7.15 (m, 13H), 7.0 (d, 1H, J=7.5 Hz), 6.9 (dd, 1H, J=2.1, 8.7 Hz), 6.09 (br s, 1H), 5.87 (s, 2H), 4.56 (s, 2H), 4.16 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 156.1, 143.3, 137.0, 136.8, 136.6, 136.5, 136.3, 128.3, 128.0, 127.9, 127.8, 123.0, 122.7, 122.1, 120.7, 120.1, 119.5, 118.3, 115.8, 113.2, 112.0, 109.7, 95.7, 76.4, 71.1, 69.7; HRMS m/z 552.2137 calcd for $C_{35}H_{28}N_4O_3$; found 552.2161. *Topsentin* ***2***. A solution of compound **16** (140 mg, 0.25 mmol) in EtOH (20 mL) containing 10% Pd/C (50 mg) and ammonium formate (210 mg, 3.3 mmol) was refluxed for 3 h. The reaction mixture was then cooled to rt and filtered through a pad of Celite (rinsing with CH_2Cl_2 and EtOAc). The filtrate was evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/MeOH 94:6) provided topsentin **2** (83 mg, 95%) as a yellow powder. R_f 0.24 (CH_2Cl_2/MeOH 95:5); IR (KBr, ν cm^{-1}) 3366–3283, 2926, 1582, 1527, 1458, 1429, 1238, 1105; UV (EtOH, λ_{max} nm) 208, 230, 253, 273, 375; ^1H NMR (300 MHz, 1% TFA in DMSO-d_6) δ 12.15 (d, 1H, J=2.6 Hz), 11.64 (br s, 1H), 8.84 (d, 1H, J=2.9 Hz), 8.15 (d, 1H, J=8.5 Hz), 8.11 (d, 1H, J=2.6 Hz), 8.05 (d, 2H, J=7.5 Hz), 7.96 (s, 1H), 7.53 (d, 1H, J=7.2 Hz), 7.22 (m, 2H), 7.0 (d, 1H, J=1.9 Hz), 6.86 (dd, 1H, J=8.5, 2.0 Hz); ^{13}C NMR (75 MHz, 1% TFA in DMSO-d_6) δ 174.6, 154.6, 144.0, 137.8, 136.6, 136.4, 133.4, 124.7, 124.2, 122.2, 122.0, 120.0, 119.8, 119.4, 119.0, 114.0, 112.4, 112.1, 106.1, 97.7; HRMS m/z 342.1110 calcd for $C_{20}H_{14}N_4O_2$; found 342.1116.

4.4. Synthesis of bromodeoxytopsentin 4

4.4.1. Using the BOM protecting group for the imidazole moiety

1-Benzenesulfonyl-6-bromo-3-tributylstannyl-1H-indole ***7h***. To a solution of 6-bromo-indole **7f** (1.8 g, 9.18 mmol) in dry DMF (30 mL) was added KOH (1.4 g, 25 mmol) and then a solution of I_2 (2.4 g, 9.45 mmol) in DMF (30 mL) was added dropwise. The reaction mixture was stirred at rt for 30 min and then poured onto ice. The resulting mixture was extracted with EtOAc. The organic extract was washed (diluted aq $NaSO_3H$, H_2O, brine), dried ($MgSO_4$), and evaporated to afford crude 6-bromo-3-iodoindole, which was used for the next step without further purification. To a solution of the later (2.94 g, 9.1 mmol) in dry DMF (40 mL) was added NaH (60%, 480 mg, 12 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 30 min and then a solution of $PhSO_2Cl$ (1.6 mL, 10.6 mmol) in DMF (10 mL) was added. The reaction mixture was allowed to warm to rt and stirred for 3 h. It was then poured into cold H_2O, extracted with EtOAc, washed (H_2O, brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with hexane/EtOAc 9:1) furnished 1-benzenesulfonyl-6-bromo-3-iodo-1*H*-indole **7g** (4.05 g, 95%) as a pale yellow solid. R_f 0.37 (hexane/AcOEt 9:1); mp 173–174 °C; IR (KBr, ν cm^{-1}) 3140–3126, 1585, 1421, 1367, 1176; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 1H, J=1.5 Hz), 7.89 (br d, 2H, J=7.3 Hz), 7.65 (s, 1H), 7.58 (m, 1H), 7.48 (m, 2H), 7.41 (dd, 1H, J=8.4, 1.5 Hz), 7.21 (d, 1H, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 134.8, 134.4, 131.4, 130.1, 129.6, 127.4, 126.8, 123.2, 119.6, 116.3, 66.5; HRMS m/z 460.8582 calcd for $C_{14}H_9^{79}BrINO_2S$; found 462.8584, m/z 462.8561 calcd for $C_{14}H_9^{81}BrINO_2S$; found 462.8591. To a solution of compound **7g** (600 mg, 1.3 mmol) in DMF (15 mL) was added dichlorobis(triphenylphosphine)palladium(II), $PdCl_2(PPh_3)_2$ (76 mg, 0.11 mmol), and then hexabutylditin, $(Bu_3Sn)_2$ (1 mL, 2 mmol). The reaction mixture was warmed to 100 °C and stirred at that temperature for 30 min. Then the reaction mixture was cooled to rt, diluted with Et_2O, washed (H_2O, brine), dried ($MgSO_4$), and evaporated to provide the crude stannane (1.9 g) as a colored oil, which upon flash chromatography (eluting with hexane/EtOAc/Et_3N 94:5:1) afforded pure stannane **7h** (526 mg, 64%) as a colorless oil. R_f 0.58 (hexane/AcOEt 9:1); IR (KBr, ν cm^{-1}) 2957–2928, 2852, 1592, 1446, 1417, 1373, 1184, 1130, 1091; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.88 (br d, 2H, J=7.6 Hz), 7.52 (m, 1H), 7.43 (m, 2H), 7.38 (s, 1H), 7.31 (br s, 2H), 1.51 (m, 6H), 1.31 (m, 6H), 1.13 (m, 6H), 0.86 (t, 9H, J=7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 136.5, 135.9, 133.8, 131.9, 129.3, 126.6, 126.4, 123.8, 117.9, 117.1, 116.5, 29.0, 27.1 (satellites at 27.5 and 26.7), 13.6, 9.9 (satellites at 12.1 and 7.5); HRMS m/z 625.0672 calcd for $C_{26}H_{36}^{79}BrNO_2S^{120}Sn$; found 625.0666, m/z 627.0651 calcd for $C_{26}H_{36}^{81}BrNO_2S^{120}Sn$; found 627.0784. *[4-(1-Benzenesulfonyl-6-bromo-1H-indol-3-yl)-1-benzyloxymethyl-1H-imidazol-2-yl]-(1-benzenesulfonyl-1H-indol-3-yl)-methanone* ***17***. To a solution of the iodoimidazole **10** (125 mg, 0.21 mmol) in DMF (4 mL) at rt was added $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol) and CuI (6 mg, 0.03 mmol). The reaction mixture was heated 120 °C and a solution of the stannane **7h** (160 mg, 0.256 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at 120 °C for 2 h and then allowed to return to rt. It was filtered through a pad of Celite and concentrated under vacuum. The residue was purified by flash chromatography (eluting with CH_2Cl_2/hexane 7:3) to afford compound **17** (124 mg, 73%). R_f 0.28 (CH_2Cl_2/hexane 7:3); ^1H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.46 (m, 1H), 8.16 (d, 1H, J=8.5 Hz), 8.05–7.97 (m, 3H), 7.95 (d, 1H, J=7.7 Hz), 7.61 (s, 1H), 7.60–7.45 (m, 7H), 7.38 (m, 2H), 7.29 (m, 5H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 142.6, 137.8, 137.7, 136.9, 136.6, 136.1, 134.9, 134.5, 134.4, 134.2, 129.6, 129.5, 128.6, 128.5, 128.1, 127.8, 127.4, 127.3, 127.2, 127.1, 126.8, 125.6, 124.9, 122.9, 122.7, 120.8, 119.0, 118.9, 116.7, 116.3, 115.1, 71.6; HRMS *m*/*z* 804.0712 calcd for $C_{40}H_{29}^{79}BrN_4O_6S_2$; found 804.0700, *m*/*z* 806.0691 calcd for $C_{40}H_{29}^{81}BrN_4O_6S_2$; found 806.0626. *Bromodeoxytopsentin* ***4***. To a solution of compound **17** (120 mg, 0.15 mmol) in EtOH/THF (10:2 mL) was added 10% aqueous KOH (4 mL). The reaction mixture was refluxed for 3 h and then it was allowed to return to rt, diluted with CH_2Cl_2, and washed (H_2O and brine). The organic phase was dried ($MgSO_4$) and evaporated to dryness leaving crude **18** as an oil (62 mg, 90%). Compound **18** was dissolved in a mixture of 3 N HCl/THF (2:1, 9 mL). The solution was stirred overnight under reflux, then cooled to rt and made basic by slow addition of 10% aqueous NaOH and extracted with EtOAc. The organic phase was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 9:1→4:1) led to bromodeoxytopsentin **4** (39 mg, 71%; 64% from **17**). R_f 0.33 (CH_2Cl_2/EtOAc 4:1); ^{1}H NMR (300 MHz, 2% TFA in DMSO-d_6) δ 11.0 (br s, 1H), 10.3 (br s, 1H), 8.99 (d, 2H, *J*=3.1 Hz), 8.36 (m, 1H), 8.08 (d, 1H, *J*=2.6 Hz), 8.02 (d, 1H, *J*=8.5 Hz), 7.96 (s, 1H), 7.70 (d, 2H, *J*=1.8 Hz), 7.60 (m, 1H), 7.36–7.25 (m, 3H); ^{13}C NMR (75 MHz, 2% TFA in DMSO-d_6) δ 173.0, 142.3, 138.8, 137.8, 137.2, 131.6, 126.6, 126.4, 124.4, 123.7, 123.5, 123.2, 121.76, 121.70, 117.4, 115.4, 115.2, 114.0, 113.1, 104.4; HRMS *m*/*z* 404.02907 calcd for $C_{20}H_{13}^{79}BrN_4O$; found 404.02727, *m*/*z* 406.02522 calcd for $C_{20}H_{13}^{81}BrN_4O$; found 406.01652.

4.4.2. Using a SEM protecting group for the imidazole moiety

4-Iodo-[2-(trimethylsilyl)ethoxy]methyl-1H-imidazole-2-carboxaldehyde ***8d***. To a solution of 4,5-diiodoimidazole (500 mg, 1.56 mmol) in DMF (20 mL) at 0 °C was added NaH (60%, 100 mg, 2.5 mmol) in small portions. After stirring at that temperature for 30 min, 2-(trimethylsilyl)ethoxymethylchloride SEMCl (0.4 mL, 2.3 mmol) was added dropwise. The reaction mixture was allowed to warm slowly to rt and stirred for 3 h. It was then diluted with Et_2O and washed (saturated $NaCO_3H$, H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure to provide an oily residue (711 mg). Flash chromatography of the oily residue (eluting with CH_2Cl_2/EtOAc 97:3) led to 4,5-diiodo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole[4b] (510 mg, 72%). To a solution of that SEM-protected imidazole derivative (2 g, 4.4 mmol) in THF (25 mL) at −78 °C was added *n*-BuLi (2.5 M, 2.2 mL). The solution was stirred at that temperature for 45 min and the lithium derivative thus formed was quenched by addition of DMF (2 mL). The reaction mixture was allowed to warm to rt and then treated with a saturated NH_4Cl aqueous solution and EtOAc. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 97.5:2.5) furnished the aldehyde **8d** (710 mg, 45%) as a pale yellow oil. IR (KBr, ν cm^{-1}) 1689, 1402, 1250, 1097, 943, 860, 837; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.4 (s 1H), 5.68 (s, 2H), 3.51 (t, 2H, *J*=9 Hz), 0.86 (t, 2H, *J*=9 Hz), −0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 144.9, 130.6, 85.3, 75.8, 67.2, 17.6, −1.6; HRMS *m*/*z* 352.0104 calcd for $C_{14}H_8IN_2O_2Si$; found 352.0096. *(1-Benzenesulfonyl-1H-indol-3-yl)-[4-iodo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-methanol* ***19***. To a solution of 1-benzenesulfonyl-3-iodo-1*H*-indole **7b** (1 g, 2.6 mmol) in dry THF (24 mL) under argon at −90 °C (liquid nitrogen/MeOH) was added ^{t}BuLi (1.7 M in pentane, 3.6 mL) and the reaction mixture was stirred at that temperature for 5 min. To the resulting solution of 3-lithio-derivative **7i** was added a solution of aldehyde **8d** (480 mg, 1.36 mmol) in THF (6 mL). The reaction mixture was slowly warmed to −20 °C (over 2 h), quenched at that temperature with saturated aqueous NH_4Cl, and then extracted at rt with CH_2Cl_2. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 98:2→94:6) afforded the secondary alcohol **19** (440 mg, 53%) as a colorless oil. R_f 0.16 (CH_2Cl_2/AcOEt 97.5:2.5); IR (KBr, ν cm^{-1}) 3400–3100, 2953–2895, 2361, 2341, 1599, 1448, 1373, 1176, 1118, 1099; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H, *J*=6.3 Hz), 7.9 (d, 2H, *J*=7.5 Hz), 7.71 (br d, 1H, *J*=1.0 Hz), 7.53 (m, 1H), 7.41 (m, 2H), 7.28 (m, 2H), 7.13 (br t, 1H, *J*=7.5 Hz), 7.01 (s, 1H), 6.16 (br d, 1H, *J*=2 Hz), 5.62 (br d, 1H, *J*=5.2 Hz), 5.11 (d, 1H, *J*=10.5 Hz), 5.04 (d, 1H, *J*=10.5 Hz), 3.11 (m, 2H), 0.63 (m, 2H), −0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 138.0, 135.5, 133.9, 129.3, 128.3, 126.6, 126.3, 125.1, 123.8, 123.6, 122.4, 120.2, 113.6, 79.5, 75.2, 66.8, 63.8, 17.6, −1.6; HRMS *m*/*z* 609.0614 calcd for $C_{24}H_{28}IN_3O_4SSi$; found 609.0628. *(1-Benzenesulfonyl-1H-indol-3-yl)-[4-iodo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-methanone* ***20***. To a solution of alcohol **19** (385 mg, 0.63 mmol) in CH_2Cl_2 (30 mL) was added MnO_2 (1.1 g, 12 mmol) and the resulting suspension was stirred for 3 h at rt. The reaction mixture was filtered (rinsing with CH_2Cl_2) and the filtrate was evaporated leading to essentially pure compound **20** (357 mg, 93%) as colorless oil. R_f 0.48 (CH_2Cl_2/hexane 4:1); IR (KBr, ν cm^{-1}) 1634, 1530, 1446, 1383, 1176, 1099, 976, 1176, 858; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.42 (m, 1H), 8.02 (m, 3H), 7.6 (m, 1H), 7.53 (m, 2H), 7.51 (s, 1H), 7.38 (m, 2H), 5.84 (s, 2H), 3.65 (m, 2H), 0.97 (m, 2H), −0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 144.6, 137.6, 134.4, 129.5, 128.6, 127.2, 125.6, 124.8, 122.8, 118.8, 113.1, 83.0, 77.4, 67.5, 17.8, −1.5; HRMS *m*/*z* 607.0458 calcd for $C_{24}H_{26}IN_3O_4SSi$; found 607.0458. *[4-(1-Benzenesulfonyl-6-bromo-1H-indol-3-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-(1-benzenesulfonyl-1H-indol-3-yl)-methanone* ***21***. To a solution of the iodo-imidazole **20** (315 mg, 0.52 mmol) in DMF (12 mL) were added, under argon, $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol) and CuI (20 mg, 0.1 mmol). Then a solution of the stannane **7h** (525 mg, 0.84 mmol) in DMF (3 mL) was added dropwise. The reaction mixture was heated under argon and stirred at 120 °C for 2 h, then it was allowed to return to rt and filtered through a pad of Celite (rinsing with CH_2Cl_2). The filtrate was concentrated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/hexane 3:1) afforded compound **21** (217 mg, 51%) as a pale yellow syrup. R_f 0.34 (CH_2Cl_2/hexane 3:1); IR (KBr, ν cm^{-1}) 1633, 1448, 1377, 1184, 1136, 1091, 976, 1176, 858; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.6 (s, 1H), 8.48 (m, 1H), 8.29 (d, 1H, *J*=1.6 Hz), 8.22 (d, 1H, *J*=8.5 Hz), 8.2–7.95 (m, 6H), 7.69 (s, 1H), 7.65–7.45 (m, 7H), 7.40 (m, 2H), 5.97 (s, 2H), 3.71 (m, 2H), 1.02 (m, 2H), −0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 142.5, 137.8, 137.7, 136.1, 134.9, 134.5, 134.4, 134.2, 129.6, 129.5, 128.7, 127.5, 127.3, 127.1, 126.6, 125.6, 124.8, 122.9, 120.5, 119.0, 116.7, 116.4, 113.0, 77.3, 67.3, 17.9, −1.4; HRMS *m*/*z* 814.0950 calcd for $C_{38}H_{35}^{79}BrN_4O_6S_2Si$; found 814.0924, *m*/*z* 816.0930 calcd for $C_{38}H_{35}^{81}BrN_4O_6S_2Si$; found 816.0831. *[4-(6-Bromo-1H-indol-3-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-(1H-indol-3-yl)-methanone* ***22***. To a solution of compound **21** (180 mg, 0.22 mmol) in EtOH/THF (10 mL:2 mL) was added 10% aqueous KOH (4 mL). The reaction mixture was refluxed for 2.5 h, cooled back to rt, diluted with EtOAc, and washed (H_2O and brine). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 9:1) furnished compound **22** (105 mg, 89%) as a yellow syrup; IR (KBr, ν cm^{-1}) 3395–3308, 1597, 1518, 1452, 1425, 1095, 1078, 858, 744; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 8.71 (m, 1H), 8.60–8.53 (m, 2H), 7.83 (d, 1H, *J*=8.5 Hz), 7.49 (s, 1H), 7.36–7.11 (m, 6H), 5.92 (s, 2H), 3.70 (m, 2H), 0.98 (m, 2), −0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 143.6, 137.3, 136.9, 136.3, 136.1, 126.8, 124.1, 123.9, 123.7, 123.1, 123.0, 122.5, 121.2, 118.8, 116.3, 116.0, 114.7, 111.9, 110.8, 77.0, 67.2, 18.1, −1.3; HRMS *m*/*z* 534.1086 calcd for $C_{26}H_{27}^{79}BrN_4O_2Si$; found 534.1089, *m*/*z* 536.1066 calcd for $C_{26}H_{27}^{81}BrN_4O_2Si$; found 536.1077. *Deoxybromotopsentin* ***4***. The SEM-protected compound **22** (87 mg, 0.16 mmol) was dissolved in a mixture of 3 N HCl/THF (2:1, 9 mL). The reaction mixture was

stirred overnight under reflux, then cooled to rt and made basic by slow addition of 10% aqueous NaOH. The alkaline reaction mixture was extracted with EtOAc. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 9:1→4:1) led to bromodeoxytopsentin **4** (42 mg, 64%, already described).

4.5. Synthesis of bromotopsentin 5

*4.5.1. 1-Benzenesulfonyl-3-iodo-6-methoxymethoxy-1H-indole **7i***

To a solution of 4-hydroxybenzaldehyde (6 g, 49 mmol) in CH_2Cl_2 (50 mL) maintained around 0 °C in a cooling bath were added $^{i}Pr_2NEt$ (19 mL, 110 mmol) and methoxymethylchloride, MOMCl (5 mL, 65 mmol). The reaction mixture was allowed to warm and stirred at rt for 1.5 h and then diluted with CH_2Cl_2, washed (1 N HCl, saturated $NaHCO_3$, H_2O, and brine), and evaporated under reduced pressure. Purification of the residue by flash chromatography (eluting with CH_2Cl_2/EtOAc 95:5) led to 4-(methoxymethyl)oxy-benzaldehyde (7.7 g, 94%). A mixture of ethylazidoacetate (9.7 g, 75 mmol) and 4-OMOM-aldehyde (3 g, 18 mmol) in EtOH (18 mL) was added slowly (over 1.5 h) to a solution of NaOEt in EtOH (2.5 N, 30 mL) at −10 °C. Then, the reaction mixture was warmed to rt, most of the solvent was evaporated under reduced pressure, and the residue was diluted with EtOAc. The resulting solution was washed (H_2O, brine), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was dissolved in xylene (60 mL) and the solution was refluxed for 1 h. The reaction mixture was cooled to rt. Evaporation of the solvent under reduced pressure led to 6-(methoxymethoxy)-1*H*-indole-2-carboxylic acid ethyl ester (2.58 g, 57%) as a pale yellow solid. To a solution of this ester (2.38 g, 9.6 mmol) in THF/H_2O/MeOH (4:3:2, 90 mL) was added a large excess of $LiOH\cdot H_2O$ (6 g). The reaction mixture was stirred at rt for 4 h and then most of the organic solvents were removed under reduced pressure. The essentially aqueous residue was cooled to 0 °C, acidified to pH ~3 (with 5 N HCl), and extracted with EtOAc. The organic extracts were combined, washed (H_2O, brine), dried ($MgSO_4$), and evaporated under reduced pressure to provide the corresponding acid (2.1 g) as a powder. The crude acid was treated with Cu (1.4 g) in quinoline (30 mL) at reflux for 2 h. The reaction mixture was then cooled to rt, diluted with EtOAc, and filtered through Celite. The filtrate was acidified to pH ~4 with 5 N HCl (cooling by addition of ice). The organic phase was washed (saturated $NaCO_3H$ and brine), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was diluted with Et_2O, washed (1 N aqueous HCl, saturated $NaCO_3H$, and brine), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Flash chromatography of the residue (eluting with hexane/EtOAc 4:1) furnished the expected 6-methoxymethoxy-1*H*-indole (952 mg, 56%) as a pale yellow oil. R_f 0.33 (hexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.5 (d, 1H, J=8.6 Hz), 7.02–6.98 (m, 2H), 6.87 (dd, 1H, J=8.6, 2.2 Hz), 6.45 (m, 1H), 5.2 (s, 2H), 3.5 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 136.2, 123.6, 123.1, 121.0, 111.2, 102.1, 98.1, 95.3, 55.8. To a solution of indole (860 mg, 4.86 mmol) in dry DMF (8 mL) was added KOH (700 mg, 12.5 mmol) and, after 5 min of stirring at rt, a solution of I_2 (1.3 g, 5.1 mmol) in DMF (25 mL) was added dropwise. The reaction mixture was stirred at rt for 30 min and then poured into cold H_2O and extracted with EtOAc. The organic extract was washed (diluted aq $NaSO_3H$, H_2O, brine), dried ($MgSO_4$), and evaporated under reduced pressure. To a solution of the crude 6-(methoxymethyl)oxy-3-iodoindole (1.1 g) in dry THF/DMF (35 mL, 2.5:1) was added NaH (60%, 190 mg, 4.7 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 10 min and then a solution of $PhSO_2Cl$ (0.7 mL, 4.6 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to rt and stirred for 2 h. It was then poured into cold H_2O, extracted with CH_2Cl_2, washed (saturated $NaCO_3H$, H_2O, brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with hexane/EtOAc 4:1) furnished compound **7i** (1.5 g, 71%) as a thick oil. R_f 0.38 (hexane/EtOAc 4:1); IR (KBr, ν cm^{-1}) 3142, 1612, 1579, 1487, 1184, 1446, 1371, 1176; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.68 (d, 1H, J=2.0 Hz), 7.6 (s, 1H), 7.56 (m, 1H), 7.45 (m, 2H), 7.24 (d, 1H, J=8.6 Hz), 7.03 (dd, 1H, J=8.6, 2.1 Hz), 5.24 (s, 2H), 3.5 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 137.5, 134.8, 134.0, 129.2, 127.1, 126.9, 122.5, 114.4, 100.8, 95.0, 66.7, 56.0; HRMS m/z 442.9688 calcd for $C_{16}H_{14}INO_4S$; found 442.9689.

*4.5.2. Synthesis of **5** using the SEM protecting group for the imidazole moiety*

*(1-Benzenesulfonyl-6-methoxymethoxy-1H-indol-3-yl)-[4-iodo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-methanol **23***. To a solution of indole **7i** (1 g, 2.26 mmol) in dry THF (25 mL) under argon at −78 °C was added ^{t}BuLi (1.7 M in pentane, 1.5 mL) and the reaction mixture was stirred at that temperature for 30 min. To the resulting solution of 3-lithio-indole **7j** was added a solution of aldehyde **8d** (740 mg, 2.1 mmol) in THF (6 mL). The mixture was slowly warmed to 0 °C (over 3 h), quenched by addition of saturated aqueous NH_4Cl, and diluted with CH_2Cl_2. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (1.63 g, eluting with hexane/EtOAc 6:4) afforded the secondary alcohol **23** (625 mg, 44%) as a colorless oil. R_f 0.29 (hexane/EtOAc 6:4); IR (KBr, ν cm^{-1}) 3134–2953, 1614, 1485, 1373, 1184, 1101; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (br d, 2H, J=7.3 Hz), 7.70 (d, 1H, J=2.1 Hz), 7.64 (d, 1H, J=1.2 Hz), 7.56 (m, 1H), 7.45 (m, 2H), 7.14 (d, 1H, J=8.7 Hz), 7.04 (s, 1H), 6.88 (dd, 1H, J=8.7, 2.1 Hz), 6.15 (br s, 1H), 5.77 (m, 1H, exchangeable with D_2O), 5.23 (d, 1H, J=6.7 Hz), 5.20 (d, 1H, J=6.7 Hz), 5.15 (d, 1H, J=10.5 Hz), 5.08 (d, 1H, J=10.5 Hz), 3.51 (s, 3H), 3.14 (m, 2H), 0.69 (m, 2H), −0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 150.1, 137.8, 136.2, 133.8, 129.2, 126.9, 123.0, 122.2, 120.7, 113.9, 101.4, 94.9, 79.3, 75.1, 66.6, 63.7, 55.9, 17.6, −1.6; HRMS m/z 669.0825 calcd for $C_{26}H_{32}IN_3O_6SSi$; found 669.0808. *(1-Benzenesulfonyl-6-methoxymethoxy-1H-indol-3-yl)-[4-iodo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-methanone **24***. To a solution of alcohol **23** (500 mg, 0.75 mmol) in CH_2Cl_2 (75 mL) was added MnO_2 (1.5 g, 17 mmol) and the resulting suspension was stirred for 3 h at rt. The reaction mixture was filtered (rinsing with CH_2Cl_2) and the filtrate was evaporated under reduced pressure leading to essentially pure compound **24** (432 mg, 87%) as a colorless syrup. R_f 0.59 (hexane/EtOAc 6:4); IR (neat, ν cm^{-1}): 1630, 1529, 1448, 1383, 1186, 1099, 985; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.2 (s, 1H), 8.28 (d, 1H, J=8.8 Hz), 8.03 (br d, 2H, J=7.5 Hz), 7.69 (d, 1H, J=2.1 Hz), 7.59 (m, 1H), 7.50 (m, 2H), 7.45 (s, 1H), 7.1 (dd, 1H, J=8.8, 2.2 Hz), 5.83 (s, 2H), 5.24 (s, 2H), 3.64 (t, 2H), 3.5 (s, 3H), 1.07 (m, 2H), −0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 155.8, 144.5, 137.4, 135.1, 134.4, 129.5, 127.3, 123.4, 123.1, 116.7, 115.0, 100.7, 94.9, 82.9, 77.3, 67.4, 56.0, 17.8, −1.5; HRMS m/z 667.0669 calcd for $C_{26}H_{30}IN_3O_6SSi$; found 667.0655. *[4-(1-Benzenesulfonyl-6-bromo-1H-indol-3-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-(1-benzenesulfonyl-6-methoxymethoxy-1H-indol-3-yl)-methanone **25***. To a solution of the iodo-imidazole **24** (290 mg, 0.43 mmol) in DMF (12 mL) were added, under argon, $PdCl_2(PPh_3)_2$ (30 mg, 0.04 mmol) and CuI (20 mg, 0.1 mmol). Then a solution of the stannane **7h** (320 mg, 0.51 mmol) in DMF (3 mL) was added dropwise. The reaction mixture was heated at 120 °C under argon and stirred at the same temperature for 2 h, then allowed to return to rt and filtered through a pad of Celite (rinsing with CH_2Cl_2). The filtrate was concentrated under reduced pressure. Flash chromatography of the residue (eluting with hexane/EtOAc 7:3) afforded compound **25** (250 mg, 66%) as a yellow powder. R_f 0.35 (CH_2Cl_2/hexane 3:1); IR (KBr, ν cm^{-1}) 1626, 1377, 1448, 1178, 1091, 985; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.5 (s, 1H), 8.34 (d, 1H, J=8.8 Hz), 8.27 (d, 1H, J=1.6 Hz), 8.22 (d, 1H,

J=8.5 Hz), 8.05 (d, 2H, J=7.7 Hz), 7.97 (d, 2H, J=7.7 Hz), 7.96 (s, 1H), 7.74 (d, 1H, J=2.1 Hz), 7.71 (s, 1H), 7.62–7.43 (m, 7H), 7.11 (dd, 1H, J=8.8, 2.1 Hz), 5.94 (s, 2H), 5.27 (s, 2H), 3.72 (m, 2H), 3.52 (s, 3H), 1.02 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 155.7, 142.3, 137.7, 137.4, 136.01, 135.96, 135.0, 134.7, 134.5, 134.1, 129.5, 129.4, 127.2, 127.0, 126.5, 123.3, 123.0, 122.7, 122.5, 120.4, 118.9, 116.3, 116.2, 114.7, 100.6, 94.9, 77.2, 67.1, 55.9, 17.8, −1.5; HRMS m/z 874.1162 calcd for $C_{40}H_{39}^{79}BrN_4O_8S_2Si$; found 874.1166. Anal. Calcd for $C_{40}H_{39}BrN_4O_8S_2Si$: C, 54.85; H, 4.49; N, 6.40. Found: C, 54.87; H, 4.41; N, 6.29. *[4-(6-Bromo-1H-indol-3-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-(6-methoxymethoxy-1H-indol-3-yl)-methanone* ***26***. To a solution of compound **25** (170 mg, 0.194 mmol) in EtOH/THF (10:3, 13 mL) was added 10% aqueous KOH (5 mL). The reaction mixture was refluxed for 2.5 h, cooled to rt, and diluted with EtOAc. The organic phase was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 85:15) furnished compound **26** (109 mg, 95%) as a yellow fluffy powder. R_f 0.14 (CH_2Cl_2/EtOAc 9:1); IR (neat, ν cm^{-1}) 2953–2893, 1597, 1518, 1448, 1151, 1072; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (br s, 1H), 9.14 (br s, 1H), 8.47–8.38 (m, 3H), 7.69 (br d, 1H, J=8.5 Hz), 7.45 (s, 1H), 7.23 (br d, 1H, J=8.5 Hz), 7.08–6.99 (m, 3H), 6.82 (br s, 1H), 5.86 (s, 2H), 5.08 (s, 2H), 3.66 (m, 2H), 3.48 (s, 3H), 0.95 (m, 2H), −0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 154.4, 143.3, 137.1, 136.8, 136.4, 136.0, 123.7, 123.2, 123.0, 121.6, 120.6, 118.6, 115.9, 115.6, 114.7, 113.9, 109.9, 98.5, 94.9, 76.7, 67.0, 56.0, 17.8, −1.6; HRMS m/z 594.1297 calcd for $C_{28}H_{31}^{79}BrN_4O_4Si$; found 594.1202, m/z 596.1277 calcd for $C_{28}H_{31}^{81}BrN_4O_4Si$; found 596.1143. Anal. Calcd for $C_{28}H_{31}BrN_4O_4Si$: C, 56.47; H, 5.25; N, 9.41. Found: C, 56.37; H, 5.21; N, 9.24. *Bromotopsentin* ***5***. Compound **26** (92 mg, 0.15 mmol) was dissolved in a mixture of 3 N HCl/EtOH (1:1, 10 mL). The reaction mixture was stirred overnight under reflux, then cooled to rt and made basic by slow addition of saturated aqueous Na_2CO_3. The alkaline reaction mixture was extracted with EtOAc. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/MeOH 92:8) led to bromotopsentin **5** (45 mg, 69%). R_f 0.27 (CH_2Cl_2/MeOH 9:1). UV (EtOH, λ_{max} nm) 238, 287, 378; IR (neat, ν cm^{-1}) 3447–3180, 1712, 1633, 1595, 1527, 1458, 1157, 1109; ^{1}H NMR (300 MHz, 1% TFA in DMSO-d_6) δ 12.21 (br s, 1H), 11.78 (br s, IH), 8.63 (d, 1H, J=3.1 Hz), 8.13 (d, 1H, J=2.6 Hz), 8.1 (d, 1H, J=8.5 Hz), 8.08 (s, 1H), 8.0 (d, 1H, J=8.6 Hz), 7.74 (d, 1H, J=1.5 Hz), 7.32 (dd, 1H, J=8.6, 1.5 Hz), 6.97 (d, 1H, J=2 Hz), 6.85 (dd, 1H, J=8.5, 2 Hz); ^{13}C NMR (75 MHz, 1% TFA in DMSO-d_6) δ 172.7, 155.2, 142.4, 138.3, 137.6, 137.5, 131.5, 126.3, 123.61, 123.2, 122.2, 121.5, 119.0, 117.2, 115.1, 115.0, 114.2, 113.0, 104.5, 98.1; HRMS m/z 420.0208 calcd for $C_{20}H_{13}^{79}BrN_4O_2$; found 420.0221, m/z 422.0185 calcd for $C_{20}H_{13}^{81}BrN_4O_2$; found 422.0201.

4.5.3. Synthesis of ***5*** *using the BOM protecting group for the imidazole moiety*

(1-Benzenesulfonyl-6-methoxymethoxy-1H-indol-3-yl)-(1-benzyl-oxymethyl-4-iodo-1H-imidazol-2-yl)-methanol ***27***. To a solution of indole **7i** (720 mg, 1.62 mmol) in dry THF (20 mL) under argon at −78 °C was added ^{t}BuLi (1.7 M in cyclohexane, 2.2 mL) and the reaction mixture was stirred at that temperature for 10 min. A solution of aldehyde **8c** (440 mg, 1.28 mmol) in THF (8 mL) was then added to the reaction mixture (solution of 3-lithio-indole **7k**). The mixture was slowly warmed to 0 °C (over 3 h), quenched by addition of saturated aqueous NH_4Cl, and diluted with CH_2Cl_2. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/EtOAc 92:8) afforded the secondary alcohol **27** (542 mg, 64%) as a colorless oil. *(1-Benzenesulfonyl-6-methoxymethoxy-1H-indol-3-yl)-(1-benzyloxymethyl-4-iodo-1H-imidazol-2-yl)-methanone* ***28***. To a solution of alcohol **27** (420 mg, 0.64 mmol) in CH_2Cl_2 (50 mL) was added MnO_2 (700 mg, 8 mmol) and the resulting suspension was stirred for 3 h at rt. The reaction mixture was filtered (rinsing with CH_2Cl_2) and the filtrate was evaporated under reduced pressure leading to essentially pure compound **28** (386 mg, 92%) as a colorless syrup. R_f 0.28 (CH_2Cl_2); IR (KBr, ν cm^{-1}) 1630, 1377, 1184, 1099, 983; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.27 (d, 2H, J=8.8 Hz), 8.02 (d, 1H, J=7.8 Hz), 7.69 (d, 1H, J=2.2 Hz), 7.58 (m, 1H), 7.49 (m, 2H), 7.41 (s, 1H), 7.35–7.22 (m, 5H), 7.07 (dd, 1H, J=8.8, 2.2 Hz), 5.80 (s, 2H), 5.22 (s, 2H), 4.60 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 155.8, 144.6, 137.4, 136.3, 136.1, 135.1, 134.4, 129.7, 129.5, 128.5, 128.2, 127.7, 127.3, 123.4, 123.1, 118.7, 115.0, 100.7, 94.9, 83.1, 76.8, 71.6, 56.0; HRMS m/z 657.0430 calcd for $C_{28}H_{24}IN_3O_6S$; found 657.0436. *[4-(1-Benzenesulfonyl-6-bromo-1H-indol-3-yl)-1-benzyloxymethyl-1H-imidazol-2-yl]-(1-benzenesulfonyl-6-methoxymethoxy-1H-indol-3-yl)-methanone* ***29***. To a solution of the iodo-imidazole **28** (342 mg, 0.52 mmol) in DMF (16 mL) were added, under argon, $PdCl_2(PPh_3)_2$ (36 mg, 0.05 mmol) and CuI (19 mg, 0.1 mmol). Then a solution of the stannane **7h** (500 mg, 0.8 mmol) in DMF (4 mL) was added dropwise. The reaction mixture was heated at 120 °C under argon and stirred at the same temperature for 2 h, then allowed to return to rt and filtered through a pad of Celite (rinsing with CH_2Cl_2). The filtrate was concentrated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/hexane 9:1) afforded compound **29** (322 mg, 71%) as a syrup. R_f 0.36 (CH_2Cl_2); IR (KBr, ν cm^{-1}) 1597, 1520, 1448, 1149, 1070, 873; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.31 (d, 1H, J=8.8 Hz), 8.24 (d, 1H, J=1.5 Hz), 8.16 (d, 1H, J=8.5 Hz), 8.02 (d, 2H, J=7.6 Hz), 7.94 (d, 2H, J=7.3 Hz), 7.90 (s, 1H), 7.71 (d, 1H, J=2.1 Hz), 7.59 (s, 1H), 7.57–7.40 (m, 7H), 7.32–7.22 (m, 5H), 7.08 (dd, 1H, J=8.8, 2.1 Hz), 6.00 (s, 2H), 5.23 (s, 2H), 4.63 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 155.8, 142.4, 137.7, 137.5, 136.6, 136.0, 135.1, 134.9, 134.5, 134.1, 129.6, 129.5, 128.4, 128.0, 127.7, 127.4, 127.2, 126.8, 123.5, 123.2, 122.9, 122.85, 120.8, 119.0, 118.9, 116.6, 116.3, 114.9, 100.7, 94.9, 77.0, 71.5, 56.0; HRMS m/z 864.0929 calcd for $C_{42}H_{33}^{79}BrN_4O_8S_2$; found 864.0923; m/z 866.0903 calcd for $C_{42}H_{33}^{81}BrN_4O_8S_2$; found 866.0936. *[1-Benzyloxymethyl-4-(6-bromo-1H-indol-3-yl)-1H-imidazol-2-yl]-(6-methoxymethoxy-1H-indol-3-yl)-methanone* ***30***. To a solution of compound **29** (280 mg, 0.32 mmol) in EtOH/THF (10:3, 13 mL) was added 10% aqueous KOH (5 mL). The reaction mixture was refluxed for 2.5 h, cooled to rt, and diluted with EtOAc. The organic phase was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/MeOH 97:3) furnished compound **30** (168 mg, 89%) as a yellow solid. R_f 0.25 (CH_2Cl_2/MeOH 98:2); IR (neat, ν cm^{-1}) 1597, 1520, 1448, 1149, 1070, 873; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (br s, 1H), 8.93 (br s, 1H), 8.43 (d, 1H, J=3 Hz), 8.38 (d, 1H, J=8.7 Hz), 7.64 (d, 1H, J=8.5 Hz), 7.35 (s, 1H), 7.26–7.14 (m, 6H), 7.06 (m, 2H), 7.00 (dd, 1H, J=8.7, 2.1 Hz), 6.78 (d, 1H, J=2.1 Hz), 5.77 (s, 2H), 5.02 (s, 2H), 4.78 (m, 2H), 3.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 154.4, 143.3, 137.1, 136.7, 136.6, 136.5, 136.1, 128.4, 128.9, 127.8, 123.7, 123.3, 123.2, 123.0, 121.7, 120.7, 118.8, 115.9, 115.6, 114.6, 113.9, 110.0, 98.6, 94.9, 76.5, 71.2, 67, 56.0; HRMS m/z 584.1059 calcd for $C_{30}H_{25}^{79}BrN_4O_4Si$; found 584.1061; m/z 586.1039 calcd for $C_{28}H_{31}^{81}BrN_4O_4Si$; found 586.1000. *Bromotopsentin* ***5***. Compound **30** (148 mg, 0.25 mmol) was dissolved in a mixture of 3 N HCl/EtOH (1:1, 10 mL). The reaction mixture was stirred overnight under reflux, then cooled to rt and made basic by slow addition of saturated aqueous Na_2CO_3. The alkaline reaction mixture was extracted with EtOAc. The organic layer was washed (H_2O and brine), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (eluting with CH_2Cl_2/MeOH 92:8) led to bromotopsentin **5** (72 mg, 68%, already described).

References and notes

1. (a) Bartik, K.; Braekman, J.-C.; Daloze, D.; Stoller, C.; Huysecom, J.; Vandevyver, G.; Ottinger, R. *Can. J. Chem.* **1987**, *65*, 2118–2121; (b) Tsuji, S.; Rinehart,

K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. *J. Org. Chem.* **1988**, *53*, 5446–5453; (c) Morris, S. A.; Andersen, R. *Can. J. Chem.* **1989**, *67*, 677–681; (d) Morris, S. A.; Andersen. *Tetrahedron* **1990**, *46*, 715–720; (e) Sakemi, S.; Sun, H. H. *J. Org. Chem.* **1991**, *56*, 4304–4307; (f) Shin, J.; Seon, Y.; Cho, K. W.; Rho, J.-R.; Sim, C. J. *J. Nat. Prod.* **1999**, *62*, 647–649; (g) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. *J. Nat. Prod.* **2000**, *63*, 447–451; (h) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; SimSim, C. J.; Im, K. S.; Jung, J. H. *J. Nat. Prod.* **2005**, *68*, 711–715; (i) Oh, K.-B.; Mar, W.; Kim, S.; Kim, J.-Y.; Oh, M.-N.; Kim, J.-G.; Shin, D.; Sim, C. J.; Shin, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4927–4931; (j) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; Jung, J. H. *J. Nat. Prod.* **2007**, *70*, 2–8; Goering, B. K. Ph.D. Dissertation, Cornell University, 1995.

2. (a) McConnell, O. J.; Saucy. G.; Jacobs R. U.S. Patent 5,290,777, 1994. (b) Wright, A. E.; Pomponi, S. A.; Roberts, J. A. Patent WO 9942092, 1999.
3. (a) Braekman, J. C.; Daloze, D.; Stoller, C. *Bull. Soc. Chim. Belg.* **1987**, *96*, 809–812; (b) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121–2133; (c) Guinchard, X.; Vallée, Y.; Denis, J.-N. *J. Org. Chem.* **2007**, *72*, 3972–3975; (d) Guinchard, X.; Vallée, Y.; Denis, J.-N. *Org. Lett.* **2007**, *9*, 3761–3764.
4. (a) Kawasaki, I.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2085–2086; (b) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887–1901; (c) Achab, S. *Tetrahedron Lett.* **1996**, *37*, 5503–5506.
5. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
6. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524; (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652.
7. (a) For dragmacidin A, B, and C see: Tonsiengsom, F.; Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Synthesis* **2006**, 49–54; (b) For (−) spongotine A see: Murai, K.; Morishita, M.; Nakatani, R.; Kubo, O.; Fujioka, H.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 8947–8949; (c) For hyrtinadine A see: Endo, T.; Tsuda, M.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2007**, *70*, 423–424; (d) For dragmacidin E see: Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 4775–4778.
8. Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. *J. Org. Chem.* **1984**, *49*, 4518–4523.
9. Groziak, M. P.; Wei, L. *J. Org. Chem.* **1991**, *56*, 4296–4300.
10. Kondo, Y.; Yoshida, A.; Sato, S.; Sakamoto, T. *Heterocycles* **1996**, *42*, 105–108.
11. Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757–761.
12. Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 2615–2618.
13. Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359–5364.
14. Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 926–932.
15. Young, E. H. P. *J. Chem. Soc.* **1958**, 3493–3494.
16. Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899–1906.
17. For example: (a) Tymiak, A. A.; Rinehart, K. L., Jr.; Bakus, G. J. *Tetrahedron* **1985**, *41*, 1039–1047; (b) Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem.* **1992**, *57*, 4772–4775; (c) Hughes, T. V.; Cava, M. P. *Tetrahedron Lett.* **1998**, *39*, 9629–9630; (d) Hu, J.-F.; Schetz, J. A.; Kelly, M.; Peng, J.-N.; Ang, K. K. H.; Flotow, H.; Leong, C. Y.; Ng, S. B.; Buss, A. D.; Wilkins, S. P.; Hamann, M. T. *J. Nat. Prod.* **2002**, *65*, 476–480.
18. Anwer, M. K.; Sherman, D. B.; Roney, J. G.; Spatola, A. F. *J. Org. Chem.* **1989**, *54*, 926–932.
19. Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491–3494.
20. Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891–1894.
21. Meyers, A. I.; Durandetta, J. L.; Manavu, R. *J. Org. Chem.* **1975**, *40*, 2025–2029.
22. Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1333–1337.
23. (a) Naidu, M. S. R.; Bensusan, H. B. *J. Org. Chem.* **1968**, *33*, 1307–1309; (b) Seley, K. L.; Salim, S.; Liang, Z.; O'Daniel, P. I. *J. Org. Chem.* **2005**, *70*, 1612–1619.