Total Synthesis of the Resorcylic Lactone-Based Kinase Inhibitor L-783277

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Abstract: The total synthesis of the natural product L-783277 (**1**) has been accomplished based on the convergent assembly of building blocks **9**, **10**, and **14**. Key steps are the Suzuki coupling of olefin **11** and aromatic building block **14**, the Mitsunobu-based macrolactonization of seco acid **16**, and the allylic oxidation of the macrocyclic triol **2** with polymer-bound IBX. Only one of the two C6′-stereoisomers of **2** provided L-783277 (**1**) with high selectivity.

Key words: kinase inhibitor, L-783277, natural products, resorcylic lactone, stereoselectivity, total synthesis

The interference with cellular signaling pathways or cell-cycle progression through inhibition of disease-relevant kinases represents a major paradigm in modern drug discovery.[1] In particular, several kinase inhibitors have been successfully developed in recent years for the clinical treatment of different types of cancers. While the majority of these agents (as well as others currently in clinical development) are low-molecular-weight synthetic molecules based on different types of heteroaromatic or urea scaffolds,[2,3] a number of naturally occurring resorcylic acid lactones (RAL) have recently emerged as alternative new lead structures for kinase inhibition.[4] This group of natural products includes hypothemycin,[5] LL-Z1640-2,[6] radicicol A,[7] and L-783277 (**1**)[8] (Figure 1), all of which incorporate a *cis*-enone moiety as part of their macrolactone ring.

High potency kinase inhibition by these compounds is associated with 1,4-addition of an active-site Cys residue to the β-carbon of the α,β-unsaturated carbonyl system.[8,9] Thus, kinases that do not contain a Cys residue as part of their ATP binding site are significantly less prone to inhibition by *cis*-enone-containing RAL, which confines the number of potential targets to ca. 10% of the human kinome. However, as many members of this subgroup are highly disease relevant, this limited target number in fact represents a 'built-in' specificity advantage of covalent RAL-based kinase inhibitors.

Given their interesting biological properties, *cis*-enone-containing RAL have also become important targets for total synthesis, although the chemical exploration of these systems is still somewhat limited. Total syntheses have been achieved for hypothemycin,[10] LL-Z1640-2,[10,11] and, most recently, for radicicol A,[12] but no efforts on the total synthesis of L-783277 (**1**), which is a highly potent inhibitor of MEK1,[8] have yet been reported. In this communication we disclose the first total synthesis of L-783277 (**1**), which provides the chemical foundation for future SAR studies on this lead structure.

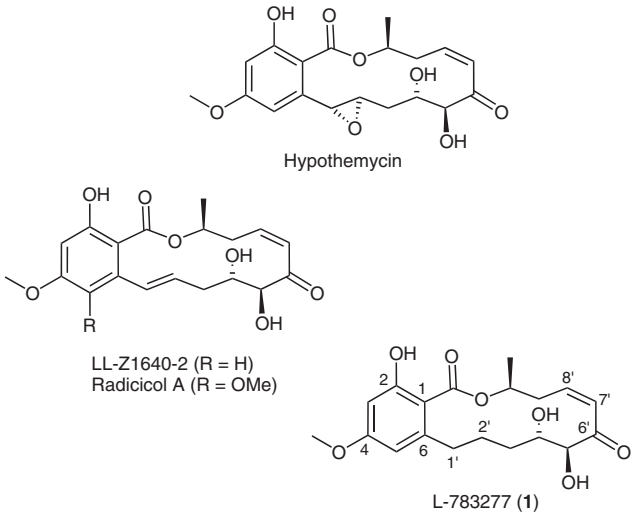

Figure 1

As illustrated by the retrosynthesis shown in Scheme 1, one of the key features of our strategy towards **1** would be the late introduction of the ketone moiety at C6′ through selective allylic oxidation of triol **2**.[11,12] The latter would be obtained from intermediate **I-1** via partial hydrogenation of the triple bond, selective removal of protecting groups, and Mitsunobu-based macrolactonization. Intermediate **I-1** was envisaged to be the result of a Suzuki coupling between an *ortho*-halo ester **I-2** and the protected C1′–C10′ fragment **I-3**, which would in turn be accessible through addition of the acetylide anion derived from **I-4** to aldehyde **I-5**.

The synthesis of building block **I-5** (Scheme 1) was initially envisioned to be based on Sharpless asymmetric dihydroxylation of a suitably protected olefin precursor (Scheme 2).

To this end, 1-pentyn-5-ol (**3**) was elaborated into the protected α,β-unsaturated ester **4** via THP protection, methoxycarbonylation, and Lindlar hydrogenation of the triple bond in excellent overall yield (92%). Treatment of **4** with AD-mix-β[13] gave the dihydroxylation product **5** in quantitative yield, but the ee of this material was only 44%.[14] In light of this stereochemical outcome, and rather than relying on the possibility of diastereomer separation at a later stage of the synthesis (which would inevitably be

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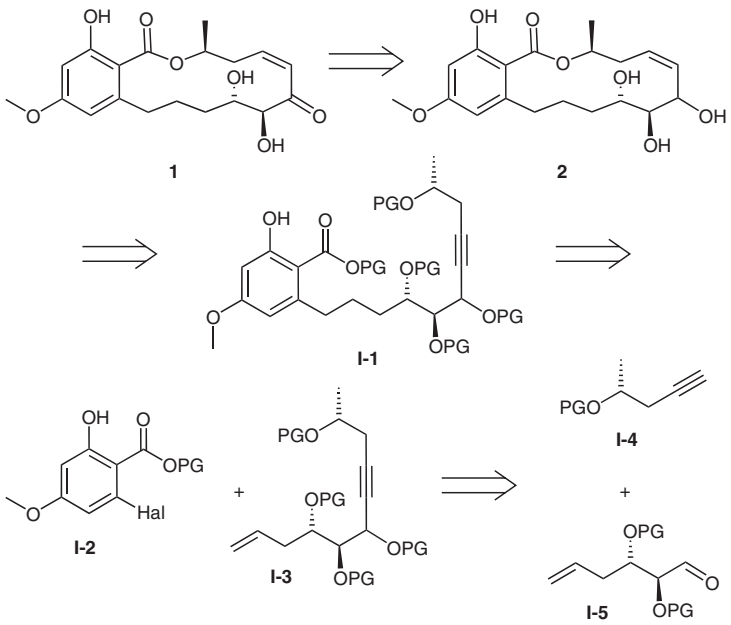
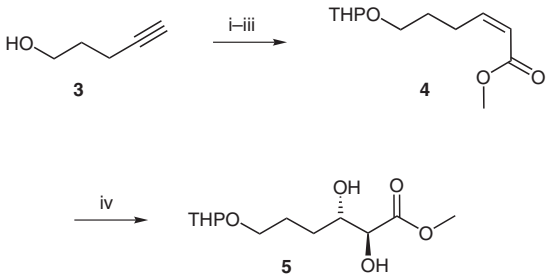


Scheme 1 Retrosynthesis of L-783277 (**1**); PG = protecting groups; these groups may vary independently



Scheme 2 *Reagents and conditions*: (i) DHP, CSA, CH_2Cl_2, 0 °C to r.t., 3 h, quant.; (ii) *n*-BuLi, MeOC(O)Cl, THF, –78 °C to –30 °C, 1 h, quant.; (iii) H_2, Lindlar catalyst, EtOAc, 1 h, 92%; (iv) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH–H_2O (1:1), 0 °C, 15 h, quant., 44% ee.

associated with a reduced overall yield), we have pursued an alternative route to intermediate **I-5** that relied on isopropylidene-D-erythrono-1,4-lactone (**6**)[15] as a chiral starting material (Scheme 3).

Thus, reduction of **6** to the corresponding lactol followed by Wittig olefination and hydrogenation of the ensuing double bond gave protected ester **7** in 80% overall yield.[16] Protection of the free hydroxyl group as a TBS ether and subsequent reduction of the ester moiety with DIBAL-H gave alcohol **8**, which was then further elaborated into aldehyde **9** (corresponding to **I-5**) via Grieco–Sharpless olefination,[17] TBS removal, and Swern oxidation (54% yield for the three-step sequence from **8**). Aldehyde **9** was then submitted to a 5-carbon extension by reaction with the anion derived from O-TBS-protected (*R*)-1-pentyn-4-ol **10** [obtained from Li-acetylide and (*R*)-methyloxirane and subsequent TBS protection of the addition product]. The reaction proceeded in excellent yield (87%) to produce the desired C1′–C10′ fragment as an inseparable 1.9:1 mixture of isomeric alcohols at C6′, which was converted into the corresponding mixture of C6′-*O*-MOM ethers **11** by reaction with MOMCl in the presence of catalytic amounts of TBAI. As the hydroxyl group formed upon addition of **10** to **9** was to be oxidized to a C6′ ketone in the natural product, the stereochemical outcome of the addition reaction appeared to be inconsequential (in principle; see, however, below).

One of the steps that we felt during the planning stage of the synthesis would be most critical in the implementation of our strategy towards L-783277 (**1**) was the projected Suzuki coupling between the C1′–C10′ fragment **I-3** (i.e. **11**) and an appropriately protected *ortho*-halo ester **I-2** (Scheme 1). The specific building block **I-2** that we chose to utilize in this coupling step was 2-TMS-ethyl ester **14** (Scheme 4), which was obtained from the corresponding methyl ester **13**[10a] via ester cleavage with TMSOK under microwave conditions and DCC/DMAP-mediated re-esterification of the free acid with 2-TMS-ethanol.

The choice of this particular carboxyl protecting group was based on prior experience with methyl ester **12** (Figure 2), which was an intermediate in a previous (and ultimately abandoned) approach to L-783277 (**1**) and which could not be saponified without destruction of the molecule under any conditions investigated.

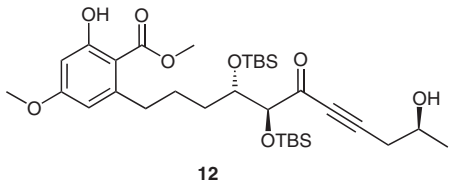
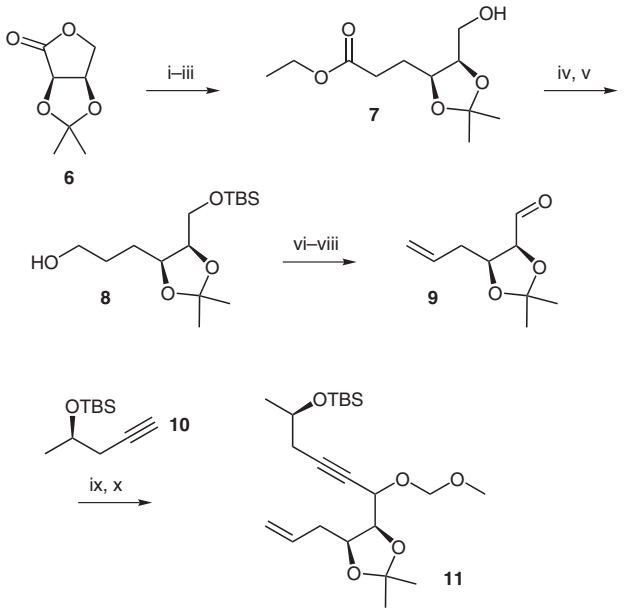
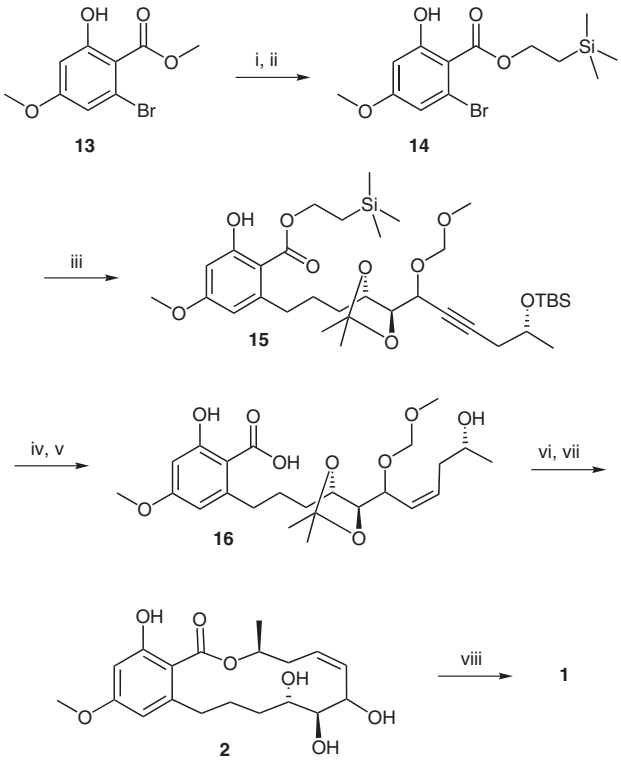


Figure 2

Of the other ester protecting groups assessed in the context of this first-generation approach, the 2-TMS-ethyl group gave the most satisfactory results and was therefore



Scheme 3 *Reagents and conditions*: (i) DIBAL-H, Et_2O, –78 °C, 2 h, 95%; (ii) $Ph_3PCHCOOEt$, dioxane, reflux, 7 h, 91% (*E*/*Z* = 1.1:1); (iii) H_2, Pd/C, EtOH, 4 h, quant.; (iv) TBSOTf, CH_2Cl_2, 93%; (v) DIBAL-H, toluene, 2 h, 85%; (vi) a. 2-$O_2NC_6H_4SeCN$, Bu_3P; b. $NaHCO_3$, 30% H_2O_2, 19 h, 81%; (vii) TBAF, THF, 0 °C to r.t., 0.5 h, 90%; (viii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, 74%; (ix) **10**, *n*-BuLi, –78 °C, 1.5 h, 87%; (x) MOMCl, $(i\text{-}Pr)_2NEt$, Bu_4NI, DMF, 19 h, 87% (1.9:1 mixture of isomers).



Scheme 4 *Reagents and conditions*: (i) TMSOK, DME, MW, 110 °C, 2 h, acidic workup, 85%; (ii) $Me_3SiCH_2CH_2OH$, DCC, DMAP, CH_2Cl_2, 15 h, 88%; (iii) a. **11**, 9-BBN, THF, r.t., 2 h; b. 2 M K_3PO_4, [$Pd(OAc)_2$ + 4 TFP], DME, reflux, 5.5 h, 81%; (iv) a. H_2, Lindlar catalyst, EtOAc, 3 h, 94%; b. separation of isomers (1.6:1); (v) TBAF, THF, r.t., 15 h, quant. (major isomer); quant. (minor isomer); (vi) DIAD, Ph_3P, toluene, 25 min, 59% (major isomer); 74% (minor isomer); (vii) sulfonic acid resin, MeOH, reflux, 6 h, 78% (major isomer); 46% (minor isomer); (viii) IBX (polymer-supported), CH_2Cl_2, r.t., 6 h; from major isomer of **2**: 1:4 product mixture of L-783277 (**1**) and a second mono-oxidized species (major product), 82% (total yield); from minor isomer of **2**: 93% of **1** (91% purity).

retained in the second-generation synthesis described here.[18] As shown in Scheme 4, the Suzuki coupling between **14** and **11**, gratifyingly, proceeded smoothly to provide the coupling product **15** in high yield (79%). Hydrogenation of **15** under Lindlar conditions gave the desired *Z*-olefin in 94% yield. At this stage, the C6′-isomers (originating from the addition reaction of **10** to **9**, vide supra) were separated and taken through the remainder of the synthesis individually. Thus, simultaneous cleavage of the TMS-ethyl ester and the TBS ether moieties with TBAF gave the seco acids **16** (in 91% and quantitative yield for the major and minor C6′-isomer, respectively), which were cyclized under Mitsunobu conditions (with concomitant inversion of configuration at C10′).[19] Subsequent deprotection with sulfonic acid resin gave the fully deprotected macrolactones **2**, which were both submitted to oxidation with polymer-bound IBX.[12,20]

Under the oxidation conditions[19] the major C6′-isomer of **2** led to a 1:4 mixture of L-783277 (**1**) and a second mono-oxidized product, whose exact structure has not been assigned at this point (82% total yield after flash chromatography). In contrast, the minor C6′-isomer of **2** gave L-783277 (**1**) in 93% yield and 91% HPLC purity, together with 8% of a second mono-oxidation product that could not be separated by TLC or flash chromatography.[21] Purification of a sample by HPLC gave L-783877 (**1**) with >95% final purity. The NMR spectra of this material were indistinguishable from those of L-783277 (**1**) from natural sources.

While the compound has been reported to be highly sensitive to acidic and basic conditions,[10] we found that L-783277 (**1**) is stable in EtOH or DMSO solution even upon prolonged storage at room temperature. Thus, only 4% and 11% of the C7′–C8′ *E*-isomer of L-783277 (**1**) were observed in EtOH and DMSO solution, respectively, after 14 days. No isomerization was observed for frozen samples of DMSO solutions.

In summary, we have accomplished the first total synthesis of the resorcylic lactone kinase inhibitor L-783277 (**1**), which represents an interesting lead structure for anticancer or anti-inflammatory drug discovery. Future work will focus on improving the efficiency of the last steps of the synthesis and, based on the chemistry developed in the course of this total synthesis, on the preparation of analogues for SAR studies.

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Institute for Biomedical Research in Basel, Switzerland, for providing us with a sample of natural L-783277 (**1**).

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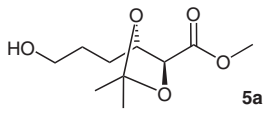
(14) The ee for the dihydroxylation product **5** was determined by chiral HPLC on a Chiralpak AD-H column after conversion into the acetonide **5a** (Figure 3) – no clean separation of enantiomers could be accomplished with **5**. *cis*-Olefins are known to give generally lower ee in AD-mix-mediated dihydroxylations than the corresponding *trans*-isomers.[13]

(15) *O*-Isopropylidene-D-erythrono-1,4-lactone (**6**) is commercially available from FLUKA.



5a

Figure 3

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(18) The use of the 2-TMS-ethyl ester group for protection of the resorcylic acid carboxylate has also been reported recently by Winssinger and co-workers as part of their synthesis of radicicol A.[12] As indicated in the text, the identification of this carboxylate protecting group as the one most suitable for our synthesis of L-783277 (**1**) occurred completely independent of Winssinger's work.

(19) Preparation and Analytical Data of Compounds **2** and **1**

Macrocyclization

To a solution of **16** (minor isomer; 10 mg, 0.021 mmol) in abs. toluene (3 mL) were added Ph_3P (11 mg, 0.043 mmol) and DIAD (9 μL, 9 mg, 0.043 mmol) and the reaction mixture was stirred at r.t. for 25 min. Filtration through Celite followed by evaporation of the filtrate and purification of the residue by flash chromatography (SiO_2 15–40 μm, Merck; hexane–EtOAc, 10:1 to 5:1) gave 7 mg (74%) of pure macrocycle.

$[\alpha]^{20}_D$ +15.3 (*c* 0.533, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.28 (m, 4 H), 1.36 (s, 3 H), 1.47 (d, *J* = 6.5 Hz, 3 H), 1.53 (s, 3 H), 2.21–2.36 (m, 2 H), 2.40–2.47 (m, 1 H), 3.20–3.27 (m, 1 H), 3.35 (s, 3 H), 3.80 (s, 3 H), 4.08 (q, *J* = 7.0 Hz, 1 H), 4.39 (d, *J* = 7.0 Hz, 1 H), 4.43–4.45 (m, 1 H), 4.53–4.65 (dd, *J* = 7.0 Hz, 2 H), 5.59–5.62 (m, 1 H), 5.92–6.09 (m, 2 H), 6.27 (d, *J* = 2.6 Hz, 1 H), 6.35 (d, *J* = 2.6 Hz, 1 H), 11.85 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.98, 22.80, 24.64, 26.89, 29.89, 30.80, 36.29, 55.46, 55.65, 67.30, 71.03, 76.85, 79.12, 92.54, 99.29, 105.67, 107.76, 110.83, 127.35, 129.71, 147.57, 164.15, 165.55, 171.30. IR (film): ν = 3734, 2934, 2361, 2341, 1732, 1645, 1614, 1456, 1375, 1255, 1210, 1159, 1094, 1032, 669 cm^{-1}. ESI-HRMS: *m/z* calcd for [M + Na]: 473.21459; found: 473.21438.

Compound 2

To a solution of the above macrocycle (115 mg, 0.256 mmol) in abs. MeOH (8.5 mL, 0.03 M) were added 247 mg (0.767 mmol) of sulfonic acid resin (Novabiochem, 3.1 mmol/g). After refluxing the mixture for 4.5 h the resin was removed by filtration, washed with MeOH, and the combined filtrates were evaporated in vacuo. Purification of the residue by flash chromatography (EtOAc–MeOH 50:1 to 30:1 to 10:1) gave 43 mg (46%) of the minor isomer of **2** as a colorless solid.

$[\alpha]^{20}_D$ +30.26 (*c* 0.542, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14–1.17 (m, 1 H), 1.34 (d, *J* = 6.4 Hz, 3 H), 1.43–1.51 (m, 1 H), 1.72–1.78 (m, 2 H), 2.10–2.17 (m, 1 H), 2.44–2.59 (m, 2 H), 2.82–2.90 (m, 1 H), 3.29 (s, 1 H), 3.32 (br s, 1 H), 3.70 (s, 3 H), 4.17 (d, *J* = 7.2 Hz, 1 H), 4.31 (d, *J* = 3.9 Hz, 1 H), 4.44–4.47 (m, 1 H), 4.49–4.50 (m, 1 H), 5.22–5.28 (m, 1 H), 5.43 (dt, *J* = 8.9 Hz, 1 H), 5.55 (dt, *J* = 11.2 Hz, 1 H), 6.23 (d, *J* = 2.3 Hz, 1 H), 6.30 (d, *J* = 2.1 Hz, 1 H), 12.14 (s, 1 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 18.00, 23.30, 29.15, 29.91, 31.91, 54.98, 67.36, 67.97, 69.42, 79.98, 98.59, 104.10, 114.90, 122.74, 133.20, 156.78, 160.86, 168.22. IR (film): ν = 3436, 2940, 2360, 2341, 1636,

1609, 1262, 1204, 1160, 1118, 1082, 1028, 991, 812 cm^{-1}. HRMS (EI): *m/z* calcd for [M + Na]: 389.15707; found: 389.15719.

L-783277 (1)

A solution of **2** (11.1 mg, 0.030 mmol) in anhyd CH_2Cl_2 (3.5 mL, 7.4 mM) was treated with 73 mg (0.081 mol) of commercially available IBX resin (Novabiochem, 1.1 mmol/g). The progress of the reaction was monitored by TLC every 15 min and workup was initiated upon complete consumption of starting material (75 min). The resin was removed by filtration, washed several times with CH_2Cl_2, and the combined filtrates were evaporated in vacuo. Purification of the residue by flash chromatography in EtOAc–MeOH (20:1) gave 10.3 mg of **1** (93%, 91% purity). This material contained 8% of a second mono-oxidized product (according to MS analysis). Purification by preparative HPLC gave 5.54 mg (50%) of **1** with >95% purity.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.23 (m, 1 H), 1.32 (d, *J* = 6.2 Hz, 3 H), 1.36–1.40 (m, 2 H), 1.56–1.60 (m, 1 H), 2.37–2.43 (m, 1 H), 2.61–2.67 (m, 2 H), 3.01–3.08 (m, 1 H), 3.73 (s, 3 H), 3.74–3.75 (m, 1 H), 4.29–4.31 (m, 1 H), 4.69 (d, *J* = 6.6 Hz, 1 H), 4.88 (d, *J* = 4.9 Hz, 1 H), 5.28–5.32 (m, 1 H), 6.20–6.25 (m, 1 H), 6.28 (d, *J* = 2.4 Hz, 1 H), 6.30 (d, *J* = 2.4 Hz, 1 H), 6.50 (dd, *J* = 11.8 Hz, 1 H). ^{13}C NMR (125.4 MHz, DMSO–d_6): δ = 19.94, 26.85, 30.94, 34.34, 35.73, 55.24, 71.19, 72.35, 81.36, 98.79, 106.90, 108.47, 127.26, 143.03, 145.06, 161.64, 162.56, 169.73, 201.74. HRMS (EI): *m/z* calcd for [M + H]: 366.1673; found: 366.1675.

(20) Polymer-bound IBX (1.1 mmol/g) was purchased from Novabiochem, Läufelfingen, Switzerland. It can also be prepared according to: Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4395.

(21) Interestingly, no differences in oxidation selectivity between C6′-isomers appear to be operative in the case of radicicol A, for which Winssinger and co-workers have reported a >90% yield for the polymer-bound IBX-mediated oxidation of the C6′-isomeric mixture of triol precursors corresponding to **2**.[12]

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