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Total Synthesis of Entecavir

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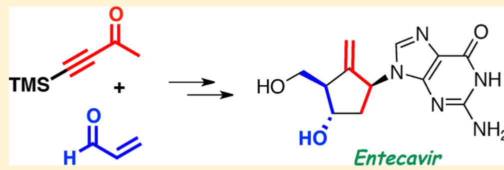
Supporting Information

ABSTRACT: Entecavir (BMS-200475) was synthesized from 4-trimethylsilyl-3-butyn-2-one and acrolein. The key features of its preparation are: (i) a stereoselective boron−aldol reaction to afford the acyclic carbon skeleton of the methylenecyclopentane moiety; (ii) its cyclization by a Cp_2TiCl-catalyzed intramolecular radical addition of an epoxide to an alkyne; and (iii) the coupling with a purine derivative by a Mitsunobu reaction.



INTRODUCTION

B-type hepatitis is a global disease. It is one of the most common viral infections worldwide despite an efficient vaccine being available since 1982. According to the World Health Organization (WHO), about two billion people are infected worldwide and 600 000 die every year due to consequences such as cirrhosis of the liver or liver cancer. Hepatitis B can manifest itself in both acute and chronic forms and is especially dangerous in children. About 90% of infants infected during the first year of life develop chronic infections, although this ratio drops to 30−50% in children infected between the ages of one and four. About 25% of adults who become chronically infected during childhood will die from hepatitis B-related liver cancer or cirrhosis while about 90% of people who become infected during adulthood will recover and be completely free of the virus within six months. About 240 million people are thought to be chronically infected with the disease worldwide.[1]

In its chronic form, hepatitis B can be treated with interferon or antiviral agents. The most frequently used antiviral agents against hepatitis B virus (HBV) are entecavir (**1**), tenofovir, adefovir, telbivudine, and lamivudine (Figure 1).[2]

Of these, entecavir is considered one of the best choices for the treatment of chronic patients due to its lack of significant adverse effects and the low risk of inducing long-term resistance to the drug.[3]

Entecavir (BMS-200475), first synthesized by Bristol-Myers Squibb,[4] was identified as a potent inhibitor of HBV in vitro (ED_{50} = 3 nM)[5] and was later commercialized as Baraclude. Its patent is due to expire in 2015 in the U.S. and soon afterward in other countries. In anticipation of the availability of a generic version, a plethora of patent applications has appeared recently.[6,8a,b] Most of the reported synthetic approaches for the stereoselective construction of the cyclopentane framework are based on transformation of a cyclopentane moiety,[6,7] and only a few start with an acyclic precursor that is subsequently cyclized.[8] In this paper, we disclose a concise synthesis of **1** from acyclic precursors.[9] As shown in Scheme 1, the retrosynthetic analysis of this carbocyclic nucleoside[10] takes advantage of the ability of epoxides to act as effective precursors of radicals. The key step involves the Ti(III)-mediated generation of a β-alkoxy carbon radical[11] from epoxide **4** that can cyclize to a methylene cyclopentane **5** through the cyclic transition state shown in Figure 2.

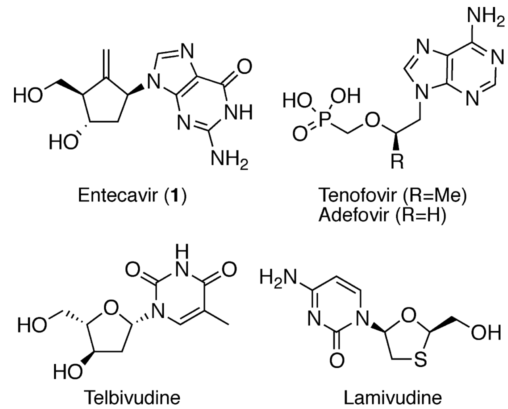


Figure 1. Antiviral agents used against HBV.

It is worth noting that the proposed radical cyclization has been reported previously in a failed attempt to prepare **1**. Thus, Ziegler[12] prepared epoxide **4b** (PG_1 = PG_2 = TBS) from protected D-glucose in 9 steps and reported very good cyclization yields when **4b** was treated with 3 equiv of Cp_2TiCl_2 in the presence of an excess of Zn in THF. Considering these precedents, we implemented an alternative route to epoxides **4** where the key step is an enantioselective acetate aldol addition[13] of methyl ketone **2** to acrolein followed by the *in situ* reduction of the corresponding β-hydroxy ketone.

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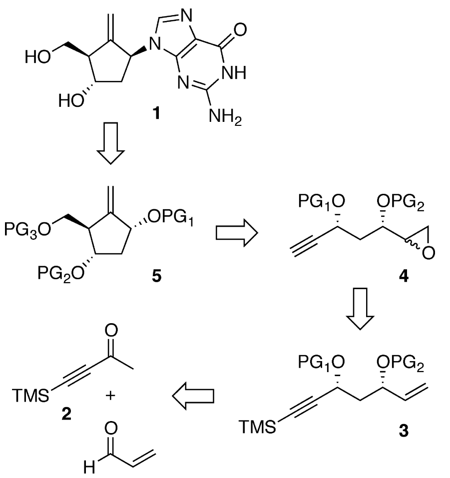
Scheme 1



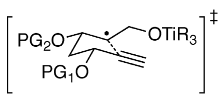


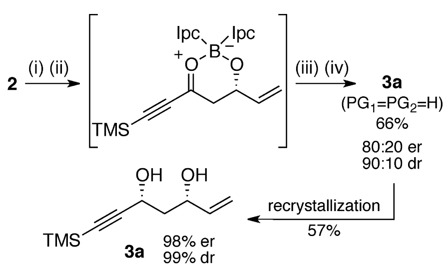
Figure 2. Proposed TS for the radical cyclization of **4**.

This approach drastically reduces the number of steps involved and potentially provides more flexibility with respect to the election of protecting groups (PG_1 and PG_2).

■ RESULTS AND DISCUSSION

The enantioselective aldol reaction of 4-trimethylsilyl-3-butyn-2-one (**2**) with acrolein was carried out using (+)-chlorodiisopinocampheylborane ((+)-DIPCl) as a source of chirality.[14] As shown in Scheme 2, the *in situ* reduction of the resulting

Scheme 2

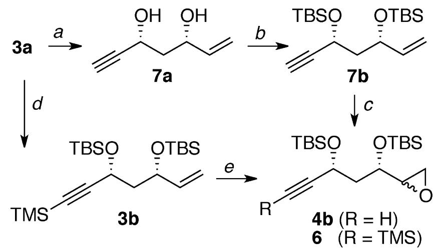


(i) (+)-DIPCl, NEt_3, THF, -5→0 °C, 2 h; (ii) acrolein, -78 °C, 1 h; (iii) $LiBH_4$, -78 °C, 1 h; (iv) H_2O_2, NaOAc, THF:H_2O, rt, 0.5 h.

chelate[15] with $LiBH_4$ followed by an oxidative work up provided **3a** (PG_1 = PG_2 = H) as a mixture of diols in 66% yield and moderate selectivity (80:20 er, 90:10 *syn*/*anti* ratio) after chromatography. It is worth noting that recrystallization from hexanes afforded pure *syn* diol **3a** (98% er, >99% dr) in 37% overall yield. Despite the low yield, this method is very straightforward and allows the skeleton of the cyclization precursor **4** to be constructed from easily available commercial starting materials in a one-pot procedure.

Conversion of **3a** into the Ziegler's epoxide **4b** or its TMS-derivative **6** is very efficient (Scheme 3). Unfortunately, the cyclization of **4b** leads to the methylene cyclopentane **5b** (PG_1 = PG_2 = TBS, PG_3 = H, Scheme 1) where the differentiation of TBS ethers would be problematic during the introduction of

Scheme 3



(a) K_2CO_3, MeOH, 1 h, rt, 98%; (b) TBSCl, imidazole, CH_2Cl_2, 15 h, rt, 95%; (c) *m*-CPBA, CH_2Cl_2, 15 h, rt, **4b**: 95%; (d) TBSCl, imidazole, CH_2Cl_2, rt, 96%; (e) *m*-CPBA, CH_2Cl_2, 15 h, rt, **6**: 91%.

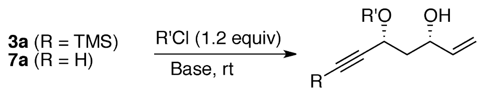
the nucleobase. On the other hand, our preliminary attempts at the cyclization of epoxide **6** led to the complete degradation of the starting material. With a view to circumventing these limitations, we evaluated the cyclization reactions for a series of epoxides of type **4** with different protecting groups (Scheme 1, $PG_1 \neq PG_2$).

Preparation of **4** ($PG_1 \neq PG_2$) from **3a** or **7a** is not trivial in some cases because there is no reliable information in the literature on the selective monoprotection of secondary propargylic alcohols in the presence of secondary allylic ones. In order to establish the viability of the monoprotection reactions, a set of silylations and benzoylations were carried out on these diols. Table 1 summarizes the optimized conditions found for each substrate and highlights the fact that protection of the propargylic position is clearly favored over the protection of the corresponding allylic position. Moderate-to-good yields of the desired monoprotected diol can be achieved while at the same time maintaining the yields of diprotected byproducts below 15%. Yields of the monoprotected allylic alcohol are less than 5%.

On the basis of these results, we attempted to prepare the diprotected epoxides **4g–j** (Scheme 4) through selective monoprotection of **3a** followed by the removal of the TMS group to afford **7c–e** monoalcohols. The sequence was completed by epoxidation with *m*-CPBA and final protection of the remaining alcohol. The alternative pathway, in which the epoxidation was the final step, was less convenient since the epoxidation of protected allylic alcohols is slow, and it is even slower with acetylated allylic alcohols. On the other hand, for the preparation of **4k** via **7f** removal of the TMS group of **3a** to afford diol **7a** was the first step in the sequence since this deprotection was not compatible with a benzoate group.

With epoxides **4g–k** in hand, we attempted to bring about their Ti(III)-mediated cyclization by treatment with Cp_2TiCl_2 in the presence of an excess of a metal M such as Zn or Mn (Scheme 5). In this type of reaction the metal reduces Cp_2TiCl_2 to a $Cp_2TiCl\cdot$ radical (**8**). Reaction of **8** with the corresponding epoxide **4** generates the titanocene(IV) β-alkoxy carbon radical **9** that gives rise to a cyclic vinyl radical **10**. This radical can then be quenched either by a hydrogen donor or by another Ti(III) radical to afford **11** or **12** (X = H or Cp_2TiCl, respectively). Protonolysis of **11**/**12** should give methylene cyclopentane **5**. Although this reaction can be catalytic in Cp_2TiCl_2, Ziegler[12] described the cyclization of epoxide **4b** using an excess of Cp_2TiCl_2. Under these conditions, however, we could not reproduce the reported yield. When epoxide **4b** was treated with Cp_2TiCl_2 in the presence of an excess of Zn following the described procedure, the methylene cyclopropane

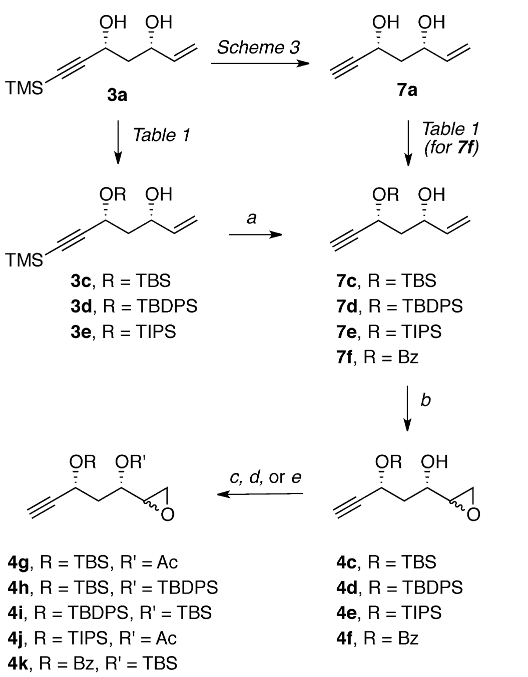
Table 1. Monoprotection of Diols 3a and 7a



entry	diol	R	R′	base	solvent	t (h)	yield (product)
1[a]	**3a**	TMS	TBS	Imidazole	THF	5	65% (**3c**)
2	**3a**	TMS	TBDPS	Imidazole	THF	5	62% (**3d**)
3	**3a**	TMS	TIPS	Imidazole	THF	15	69% (**3e**)
5[a]	**7a**	H	TBS	Imidazole	CH_2Cl_2	5	54% (**7c**)
6[a]	**7a**	H	Bz	DIPEA	CH_2Cl_2	15	86% (**7f**)

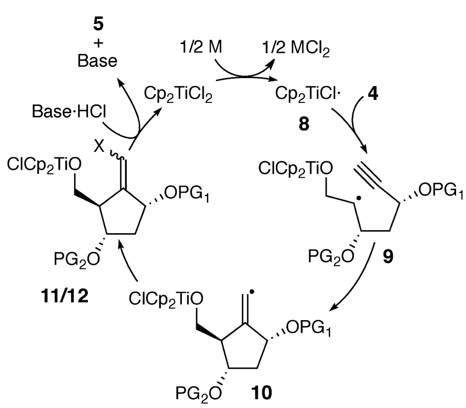
[a]R′Cl (1.1 equiv) was added.

Scheme 4



(a) **3c**, **3d** or **3e**, K_2CO_3 (0.25-0.5 equiv), MeOH, 1-3 h, rt, **7c**: 99%, **7d**: 84%,**7e**: 95%; (b) **7c-f**, *m*-CPBA (2.5-6.0 equiv), CH_2Cl_2, 2.5-15 h, rt, **4c**: 97%, **4d**: 99%, **4e**: 95%, **4f**: 87%; (c) **4c** or **4e**, Ac_2O (1.2 equiv), NEt_3, CH_2Cl_2, 1 h, rt, **4g**: 98%, **4j**: 90%; (d) **4c**,TBDPSCl (2.0 equiv), imidazole, THF, rt, 48 h, **4h**: 79%; (e) **4d** or **4f**,TBSCl (1.9-2.6 equiv), imidazole, THF, rt, 24 h, **4i**: 71%, **4k**: 67%.

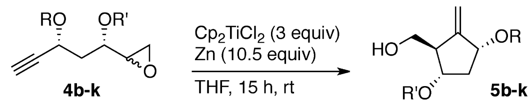
Scheme 5



5b (PG_1 = PG_2 = TBS, PG_3 = H) was obtained with good diastereoselectivity but in a yield of only 30%.

Fortunately, yields could be increased to 50% by replacing the aqueous H_2SO_4 workup with a treatment with saturated NH_4Cl (entry 1, Table 2). Under these optimized conditions,

Table 2. Stoichiometric Cyclization of Propargylic Epoxides 4b and 4g–k



entry	epoxide	R	R′	product	yield (%)	dr[a]
1	**4b**	TBS	TBS	**5b**	50	95:5
2	**4h**	TBS	TBDPS	**5h**	43	>97:3
3	**4i**	TBDPS	TBS	**5i**	<10[a]	n.d.
4	**4k**	Bz	TBS	**5k**	49	90:10
5	**4g**	TBS	Ac	**5g**	40	96:4
6	**4j**	TIPS	Ac	**5j**	0	

[a]Not chromatographically isolated. Yield estimated from ^{1}H NMR.

cyclizations of epoxides **4g–k** were carried out. The results are summarized in Table 2 and it can be seen that the election of the propargylic alcohol protecting group (R) is critical. TBS provided the best yields (entries 1, 2, and 5) when compared with TIPS and TBDPS (entries 3 and 6) and better selectivity than the benzoyl group (entry 4). In sharp contrast, protection of the allylic alcohol has little effect on yield or selectivity (entries 1, 2, and 5). These results suggested **4b**, **4g** and **4h** to be the most promising candidates for cyclization. We finally chose the transformation of **4g** to **5g** as the key step of the synthesis because it provided better overall yield from diol **3a** and allowed differentiation of the protected alcohols.

The Ti-catalytic version of the cyclization was also explored in an attempt to improve the process. In the stoichiometric process **11**/**12** are cleaved in the final step by treatment with saturated NH_4Cl. In the catalytic version an alternative proton source is required to cleave **11**/**12** and regenerate the catalyst. Gansäuer[16] described the use of collidine hydrochloride as the most convenient reagent for doing so.

After careful optimization of the reaction conditions we were able to carry out the cyclization of **4g** to **5g** using 20% catalyst and collidine hydrochloride as proton source with excellent selectivity and comparable yields to the stoichiometric version (Table 3, entries 1 and 4). Mn provides similar yields to Zn but requires less metal to generate **8**.

On the other hand, we found that the use of trimethylsilylcollidinium chloride[17] instead of collidine hydrochloride (entries 2 and 5) while not improving yields did improve the reproducibility of the process at larger scales. A further improvement was achieved by introducing Vaska's

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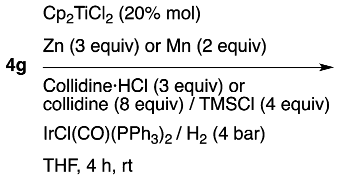
Table 3. Catalytic Cyclization of 4g to Cyclopentane 5g



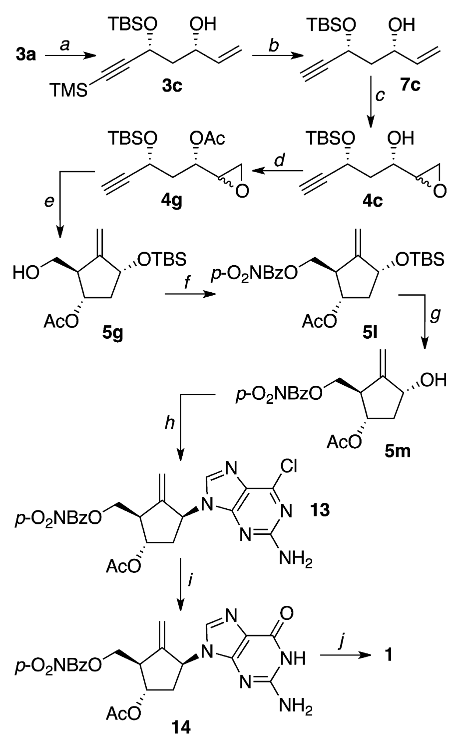
entry	M	collidinium salt	$IrCl(CO)(PPh_3)_2$	yield (%)
1	Zn	Collidine·HCl		36
2	Zn	Collidine/TMSCl		38
3	Zn	Collidine/TMSCl	5%	51
4	Mn	Collidine·HCl		42
5	Mn	Collidine/TMSCl		36
6	Mn	Collidine/TMSCl	5%	49
7	Mn	Collidine/TMSCl	10%	58

complex, $IrCl(CO)(PPh_3)_2$ in the presence of H_2 as hydrogen donor[18] (entries 3, 6, and 7).

The last step in the preparation of the carbocyclic moiety of Entecavir was the protection of the primary hydroxyl group of **5g** in the form of a *p*-nitrobenzoyl ester **5l**. The election of this protecting group is important because **5l** can be crystallized and purified. By this means, chromatographic purifications of intermediates **3a** to **5g** (which are oils) can be avoided (Scheme 6).

Final conversion of **5l** to pharmaceutical-grade Entecavir was straightforward. Selective acidic deprotection of the TBS ether followed by Mitsunobu reaction with 2-amino-6-chloropurine[6x] led to the chloroderivative **13** that was transformed into protected Entecavir **14** by treatment with formic acid. Saponification of **14** then gave Entecavir of pharmaceutical grade. Reversal of the order of the last two steps decreased the overall yield and increased the formation of impurities that impeded the crystallization of the final product as did the direct acid hydrolysis of both of the esters and the chloropurine moiety.

Scheme 6



(a) TBSCl (1.1 equiv), imidazole, THF, 6 h, rt, 69%; (b) K_2CO_3 cat., MeOH, 1 h, rt, 95%; (c) *m*-CPBA, CH_2Cl_2, 15 h, rt, 95%; (d) Ac_2O, NEt_3, DMAP cat., CH_2Cl_2, 1 h, rt, 95%; (e) Cp_2TiCl_2 20% mol., $IrCl(CO)(PPh_3)_2$ 10% mol., Mn (2 equiv), collidine, TMSCl, H_2 (4 bar), THF, 4 h, rt, 58%; (f) *p*-O_2NBzCl, NEt_3, CH_2Cl_2, 1.5 h, rt, 74%. (g) 5% (+)-CSA, MeOH, 3 h, rt, 89%. (h) 2-amino-6-chloropurine, DIAD, PPh_3, THF, 3 h, -10 °C, 61%. (i) HCOOH, 50 °C, 9h, 92%. (j) MeONa, MeOH, 1 h, rt, 72%.

■ CONCLUSIONS

A straightforward synthesis of Entecavir was achieved in 11 steps from commercially available starting materials. The cyclopentane skeleton was prepared from acyclic precursors by a boron-aldol reaction and a Ti(III)-catalyzed cyclization of an epoxide to an alkyne as key steps. The carbocyclic structure obtained in this way was attached to a purine moiety by a Mitsunobu reaction. It is worth mentioning that the use of the *p*-nitrobenzoyl group in the final steps allows purification by crystallization thus avoiding chromatography and making the synthesis amenable to scale-up. The selective hydrolysis of the 6-chloropurine unit with formic acid is also essential in order to facilitate the crystallization of the final product.

■ EXPERIMENTAL SECTION

All reactions involving moisture- or air-sensitive reagents were performed in oven-dried glassware under N_2. Chemical shifts (δ) were quoted in parts per million and referenced for ^{1}H NMR to internal TMS (for $CDCl_3$) or residual solvent peak δ 2.50 ppm (for DMSO-d_6). ^{13}C NMR was referenced to $CDCl_3$ (δ 77.0 ppm) or DMSO-d_6 (δ 39.5 ppm). Column chromatography was performed on silica gel (Merck 230−400 mesh). HRMS analyses were recorded on a LC/MSD-TOF mass spectrometer.

(3*S*,5*R*)-7-(Trimethylsilyl)hept-1-en-6-yne-3,5-diol (3a). NEt_3 (11.60 mL, 85 mmol) was added to a stirred solution of (+)−DIPCl (90−105%) (25.000 g, 78 mmol) in anhydrous THF (40 mL) under N_2 at 0 °C. 4-Trimethylsilyl-3-butyn-2-one (98%, 9.78 g, 70 mmol) was added dropwise and the mixture was stirred for 2 h at −5 to 0 °C. The solution was cooled to −78 °C and a solution of acrolein (90%, 7.62 mL, 103 mmol) in anhydrous THF (20 mL) was added slowly and the mixture was stirred for 1 h at −78 °C. A 2 M solution of $LiBH_4$ in hexanes (53 mL, 106 mmol) was added slowly and the mixture was stirred for a further 1 h at −78 °C. After careful quenching with saturated NH_4Cl (40 mL) at −78 °C the mixture was allowed to warm to rt over 30 min. After partitioning between H_2O (40 mL) and MTBE (90 mL) the aqueous layer was extracted with MTBE (25 mL). The organic phases were combined and dried ($MgSO_4$). Solvent removal afforded a pale yellow oil (62 g). THF/H_2O (3:1, 80 mL) was added under N_2 at rt followed by NaOAc (4.40 g, 54 mmol) and the mixture was cooled to 0 °C. H_2O_2 (30%, 30 mL, 5 equiv) was added dropwise over 10 min and the mixture was stirred for a further 10 min at 0 °C and 30 min at rt. After cooling to 0 °C a saturated solution of $Na_2S_2O_3$ (30 mL) was added slowly and the mixture was stirred for 10 min at 0 °C and 15 min at rt. H_2O (20 mL) and MTBE (35 mL) were added and the organic phase was decanted. The aqueous layer was extracted with MTBE (10 mL) and the combined organic extracts were dried ($MgSO_4$). Solvent removal gave a clear oil (49.2 g) that was purified by flash chromatography [silica gel, hexanes−AcOEt, from 90:10 to 60:40 (gradient elution)] to give 9.130 g of a mixture of diols (er 80:20; *syn*/*anti* 90:10).

Recrystallization from hexanes afforded the product as a white crystalline solid (**3a**,[9a] 5.2 g, 37% overall yield, er 98%). Mp 80−82 °C. $[\alpha]_D^{25}$ +2.3 (*c* 1.0, $CHCl_3$). IR (film): 3349, 2956, 2922, 2899, 2176 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.90 (ddd, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.29 (ddd, *J* = 17.2, 1.4, 1.3 Hz, 1H), 5.14 (ddd, *J* = 10.4, 1.4, 1.3 Hz, 1H), 4.64 (dd, *J* = 7.9, 5.2 Hz, 1H), 4.43−4.37 (m, 1H), 2.80 (bs, 1H), 2.46 (bs, 1H), 2.03−1.89 (m, 2H), 0.18 (s, 9H). ^{13}C NMR

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($CDCl_3$, 101 MHz): δ 140.1, 115.1, 106.1, 89.9, 72.1, 62.0, 44.0, −0.1. HRMS (ESI): *m/z* calcd for $C_{10}H_{18}O_2SiNa^+$ $[M + Na]^+$ 221.0969; found 221.0974.

(3*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-7-(trimethylsilyl)-hept-1-en-6-yne (3b). A solution of TBSCl (0.800 g, 5.30 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise to a solution of diol **3a** (0.500 g, 2.52 mmol) and imidazole (0.377 g, 5.54 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under N_2. The mixture was allowed to warm to rt and was stirred for 15 h. A 22% solution of NH_4Cl (5 mL) was added slowly and the mixture was stirred for 10 min. The mixture was partitioned and the aqueous phase was extracted with CH_2Cl_2 (5 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed affording an oil that was purified by flash chromatography (silica gel, hexanes−AcOEt 95:5) to give 1.030 g (96%) of the title compound[9a] (**3b**) as a yellow oil. $[\alpha]_D^{25}$ +21.6 (*c* 1.0, $CHCl_3$). IR (film): 3071, 2952, 2930, 2897, 2858, 2172 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.81 (ddd, *J* = 17.2, 10.3, 6.4 Hz, 1H), 5.15 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.04 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.46 (dd, *J* = 7.7, 6.4 Hz, 1H), 4.33−4.24 (m, 1H), 1.90 (ddd, *J* = 13.2, 8.1, 6.7 Hz, 1H), 1.74 (ddd, *J* = 13.2, 7.7, 5.2 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.16 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.3, 114.4, 107.4, 89.5, 71.3, 61.3, 46.9, 26.0, 25.9, 18.4, 18.3, 0.0, −4.1, −4.3, −4.8, −4.8. HRMS (ESI): *m/z* calcd for $C_{22}H_{47}O_2Si_3^+$ $[M + H]^+$ 427.2878; found 427.2867.

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(trimethylsilyl)hept-1-en-6-yn-3-ol (3c). A solution of TBSCl (4.180 g, 27.73 mmol) in anhydrous THF (20 mL) was added dropwise to a solution of diol **3a** (5.000 g, 25.21 mmol) and imidazole (2.060 g, 30.25 mmol) in anhydrous THF (60 mL) at 0 °C under N_2, and the mixture was allowed to warm to rt and was stirred for 5 h. A 22% solution of NH_4Cl (25 mL) was added slowly and the mixture was stirred for 10 min. The mixture was partitioned and the organic phase was dried ($MgSO_4$) and the solvent was removed affording an oil that was purified by flash chromatography [silica gel, hexanes−AcOEt, from 97:3 to 80:20 (gradient elution)] to give 5.123 g (65%) of the title compound[9a] (**3c**) as a pale yellow oil. $[\alpha]_D^{25}$ +39.9 (*c* 1.0, $CHCl_3$). IR (film): 3424, 3081, 2958, 2930, 2898, 2858, 2172 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.86 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.28 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.11 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.59 (dd, *J* = 7.9, 5.3 Hz, 1H), 4.42−4.30 (m, 1H), 2.98 (d, *J* = 2.4 Hz, 1H), 1.99−1.86 (m, 2H), 0.91 (s, 9H), 0.19 (s, 3H), 0.16 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.3, 114.6, 106.7, 90.3, 71.5, 62.9, 45.1, 25.9, 18.2, −0.2, −4.1, −4.8. HRMS (ESI): *m/z* calcd for $C_{16}H_{33}O_2Si_2^+$ $[M + H]^+$ 313.2014; found 313.2005.

(3*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-7-(trimethylsilyl)hept-1-en-6-yn-3-ol (3d). TBDPSCl (1.57 mL, 6.10 mmol) was added dropwise to a solution of diol **3a** (1.000 g, 5.04 mmol) and imidazole (0.481 g, 7.06 mmol) in anhydrous THF (9.5 mL) at 0 °C under N_2, and the mixture was allowed to warm to rt and was stirred for 5 h. A 22% solution of NH_4Cl (5 mL) was added slowly and the mixture was stirred for 10 min. The mixture was partitioned and the organic phase was dried ($MgSO_4$), and the solvent was removed affording an oil that was purified by flash chromatography [silica gel, hexanes−AcOEt, from 95:5 to 90:10 (gradient elution)] to give 1.363 g (62%) of the title compound (**3d**) as a pale yellow oil. $[\alpha]_D^{25}$ +62.5 (*c* 1.0, $CHCl_3$). IR (film): 3446, 3071, 2958, 2931, 2894, 2857 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77−7.66 (m, 4H), 7.45−7.33 (m, 6H), 5.84 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.23 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.07 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.54 (t, *J* = 6.3 Hz, 1H), 4.51−4.43 (m, 1H), 2.64 (d, *J* = 3.4 Hz, 1H), 2.01−1.85 (m, 2H), 1.06 (s, 9H), 0.10 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.4, 136.2, 136.0, 134.9, 133.6, 133.3, 130.0, 129.8, 129.7, 127.8, 127.7, 127.5, 114.5, 106.2, 91.3, 70.6, 62.8, 45.2, 27.0, 26.7, 19.4, −0.4. HRMS (ESI): *m/z* calcd for $C_{26}H_{37}O_2Si_2^+$ $[M + H]^+$ 437.2327; found 437.2325.

(3*S*,5*R*)-5-(Triisopropylsilyloxy)-7-(trimethylsilyl)hept-1-en-6-yn-3-ol (3e). TIPSCl (5.20 mL, 30.25 mmol) was added dropwise to a solution of diol **3a** (5.000 g, 25.21 mmol) and imidazole (2.230 g, 32.77 mmol) in anhydrous THF (40 mL) at 0 °C under N_2, and the mixture was allowed to warm to rt and was stirred for 15 h. A 22% solution of NH_4Cl (20 mL) was added slowly and the mixture was stirred for 10 min. The mixture was partitioned and the organic phase was extracted with MTBE (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed affording an oil that was purified by flash chromatography [silica gel, hexanes−AcOEt, from 97:3 to 80:20 (gradient elution)] to give 6.173 g (69%) of the title compound as a pale yellow oil. $[\alpha]_D^{25}$ +23.5 (*c* 0.6, $CHCl_3$). IR (film): 3421, 3074, 2944, 2894, 2867, 2167 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.89 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.28 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.11 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.71 (t, *J* = 6.4 Hz, 1H), 4.49−4.41 (m, 1H), 2.92 (d, *J* = 2.7 Hz, 1H), 1.95−1.89 (m, 2H), 1.27−1.13 (m, 3H), 1.13−1.04 (m, 18H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.5, 114.4, 106.9, 90.3, 71.1, 62.5, 45.5, 18.2, 17.9, 12.5, −0.2. HRMS (ESI): *m/z* calcd for $C_{19}H_{39}O_2Si_2^+$ $[M + H]^+$ 355.2483; found 355.2478.

(3*S*,5*R*)-Hept-1-en-6-yne-3,5-diol (7a). K_2CO_3 (0.348 g, 2.52 mmol) was added in one portion to a stirred solution of **3a** (1.000 g, 5.04 mmol) in anhydrous MeOH (10 mL) at rt under N_2. The mixture was then stirred for 1 h. A buffer solution (pH = 7, 10 mL) and CH_2Cl_2 (10 mL) were added, the mixture was partitioned and the organic phase was dried ($MgSO_4$). Solvent removal gave the title compound (**7a**)[12] as a yellow oil 0.628 g (98%). $[\alpha]_D^{25}$ +5.8 (*c* 1.0, $CHCl_3$). IR (film): 3347, 3290, 3060, 2983, 2953, 2922, 2887, 2113 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.86 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.26 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.11 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.61 (ddd, *J* = 8.3, 5.1, 2.1 Hz, 1H), 4.41−4.34 (m, 1H), 2.75 (bs, 1H), 2.49 (d, *J* = 2.1 Hz, 1H), 2.35 (bs, 1H), 2.03−1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.1, 115.2, 84.5, 73.3, 72.0, 61.3, 43.9. HRMS (ESI): *m/z* calcd for $C_7H_{10}NaO_2^+$ $[M + Na]^+$ 149.0573; found 149.0572.

(3*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)hept-1-en-6-yne (7b). A solution of TBSCl (2.059 g, 13.60 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise to a solution of diol **7a** (0.820 g, 6.50 mmol) and imidazole (1.062 g, 15.60 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C under N_2, and the mixture was allowed to warm to rt and was stirred for 15 h. A 22% solution of NH_4Cl (5 mL) was added slowly and the mixture was stirred for 10 min. The mixture was partitioned and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed affording an oil that was purified by flash chromatography [silica gel, hexanes−AcOEt, from 97:3 to 80:20 (gradient elution)] to give 2.280 g (95%) of the title compound (**7b**)[12] as a pale yellow oil. $[\alpha]_D^{25}$ +13.0 (*c* 1.0, $CHCl_3$). IR (film): 3306, 3093, 2958, 2930, 2887, 2858 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.81 (ddd, *J* = 17.2, 10.4, 6.5 Hz, 1H), 5.17 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.05 (dt, *J* = 10.4, 1.2 Hz, 1H), 4.47 (ddd, *J* = 8.2, 6.5, 2.0 Hz, 1H), 4.33−4.26 (m, 1H), 2.42 (d, *J* = 2.0 Hz, 1H), 1.99−1.74 (m, 2H), 0.91 (s, 9H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.3, 114.4, 85.4, 72.9, 71.1, 60.6, 47.2, 26.0, 25.9, 18.4, 18.3, −4.1, −4.4, −4.8, −4.9. HRMS (ESI): *m/z* calcd for $C_{19}H_{39}O_2Si_2^+$ $[M + H]^+$ 355.2483; found 355.2486.

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)hept-1-en-6-yn-3-ol (7c). K_2CO_3 (0.101 g, 0.73 mmol) was added in one portion to a stirred solution of **3c** (0.455 g, 1.46 mmol) in anhydrous MeOH (4.5 mL) at rt under N_2 and the mixture was stirred for 1 h. After solvent removal CH_2Cl_2 (10 mL) was added to the residue and the solution was filtered and dried ($MgSO_4$). Solvent removal gave the title compound (**7c**)[9a] as a pale yellow oil (0.366 g, 99%). $[\alpha]_D^{25}$ +32.7 (*c* 1.0, $CHCl_3$). IR (film): 3417, 3311, 3079, 2956, 2930, 2886, 2858, 2109 cm^{-1}. ($CDCl_3$, 300 MHz): δ 5.88 (ddd, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.29 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.12 (dt, *J* = 10.4, 1.5 Hz, 1H), 4.61 (ddd, *J* = 7.8, 5.8, 2.1 Hz, 1H), 4.42−4.33 (m, 1H), 2.71 (d, *J* = 2.7 Hz, 1H), 2.47 (d, *J* = 2.1 Hz, 1H), 2.03−1.85 (m, 2H), 0.92 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.3, 114.8, 84.9, 73.5, 71.2, 62.0, 45.2, 25.9, 18.2, −4.2, −4.9. HRMS (ESI): *m/z* calcd for $C_{13}H_{24}NaO_2Si^+$ $[M + Na]^+$ 263.1438; found 263.1431.

(3*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)hept-1-en-6-yn-3-ol (7d). K_2CO_3 (0.080 g, 0.57 mmol) was added in one portion to a stirred solution of **3d** (0.500 g, 1.14 mmol) in anhydrous MeOH (5

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mL) at rt under N_2 and the mixture was stirred for 3 h. A buffer solution (pH = 7, 5 mL) and MTBE (15 mL) were added, the mixture was partitioned and the organic phase was dried ($MgSO_4$). Solvent removal gave the title compound (**7d**) as a pale yellow oil (0.350 g, 84%). $[\alpha]_D^{25}$ +34.3 (*c* 1.0, $CHCl_3$). IR (film): 3453, 3303, 3071, 2956, 2930, 2891, 2858 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.78−7.69 (m, 4H), 7.47−7.36 (m, 6H), 5.88−5.78 (m, 1H), 5.22 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.08 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.60 (td, *J* = 6.5, 2.1 Hz, 1H), 4.47−4.39 (m, 1H), 2.35 (d, *J* = 2.1 Hz, 1H), 2.15 (m, 1H), 1.96−1.90 (m, 2H), 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.5, 136.2, 136.0, 133.3, 133.3, 130.4, 129.9, 127.8, 127.6, 114.6, 84.5, 74.2, 70.3, 62.1, 45.3, 27.0, 19.4. HRMS (ESI): *m/z* calcd for $C_{23}H_{28}NaO_2Si^+$ [M + Na]$^+$ 387.1751; found 387.1752.

(3*S*,5*R*)-5-(Triisopropylsilyloxy)hept-1-en-6-yn-3-ol (7e). K_2CO_3 (0.526 g, 3.81 mmol) was added in one portion to a stirred solution of **3e** (6.000 g, 15.23 mmol) in anhydrous MeOH (50 mL) at rt under N_2 and the mixture was stirred for 1 h. A buffer solution (pH = 7, 15 mL) and MTBE (15 mL) were added, the mixture was partitioned and the organic phase was dried ($MgSO_4$). Solvent removal gave the title compound (**7e**) as a pale yellow oil (4.084 g, 95%). $[\alpha]_D^{25}$ +15.7 (*c* 1.0, $CHCl_3$). IR (film): 3421, 3311, 3083, 2944, 2893, 2867 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.97−5.83 (m, 1H), 5.29 (ddd, *J* = 17.3, 2.7, 1.4 Hz, 1H), 5.12 (ddd, *J* = 10.4, 2.6, 1.4 Hz, 1H), 4.74 (td, *J* = 6.7, 2.1 Hz, 1H), 4.50−4.39 (m, 1H), 2.55 (d, *J* = 3.0 Hz, 1H), 2.49−2.46 (m, 1H), 1.99−1.91 (m, 2H), 1.24−1.06 (m, 21H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.5, 114.6, 85.0, 73.6, 70.9, 61.8, 45.5, 18.2, 18.1, 17.8, 12.4. HRMS (ESI): *m/z* calcd for $C_{16}H_{31}O_2Si^+$ [M + H]$^+$ 283.2088; found 283.2077.

(3*R*,5*S*)-5-Hydroxyhept-6-en-1-yn-3-yl benzoate (7f). *i*-Pr_2NEt (0.76 mL, 4.37 mmol) was added dropwise to a solution of **7a** (0.460 g, 3.64 mmol) in anhydrous CH_2Cl_2 (9 mL) at 0 °C under N_2. BzCl (0.46 mL, 3.96 mmol) was added dropwise at 0 °C and the mixture was warmed to rt and stirred for 15 h. MeOH (2 mL) was added and the mixture was stirred for 10 min. After solvent removal the resulting oily residue was purified by flash chromatography [silica gel, hexanes−AcOEt, from 90:10 to 80:20 (gradient elution)] to give the title compound (**7f**, as the major isomer in a 91:9 mixture of monobenzoylated regioisomers) as a pale yellow oil (0.741 g, 86%). $[\alpha]_D^{25}$ +26.0 (*c* 1.0, $CHCl_3$). IR (film): 3467, 3294, 3071, 2959, 2928, 2885, 2121, 1719 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11−8.03 (m, 2H), 7.63−7.54 (m, 1H), 7.50−7.41 (m, 2H), 5.93 (ddd, *J* = 17.1, 10.4, 6.0 Hz, 1H), 5.79 (ddd, *J* = 7.6, 6.5, 2.2 Hz, 1H), 5.30 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.17 (dt, *J* = 10.4, 1.2 Hz, 1H), 4.53−4.42 (m, 1H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.30−2.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.4, 140.0, 133.4, 129.9, 129.8, 128.5, 115.5, 81.0, 74.7, 69.9, 62.2, 41.7. HRMS (ESI): *m/z* calcd for $C_{14}H_{14}NaO_3^+$ [M + Na]$^+$ 253.0835; found 253.0837.

(1*S*,3*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-1-(oxiran-2-yl)-5-(trimethylsilyl)pent-4-yne (6). A solution of **3b** (0.900 g, 2.11 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to a suspension of *m*-CPBA (77%, 1.417 g, 6.32 mmol) in anhydrous CH_2Cl_2 (10 mL) at rt under N_2 and the mixture was stirred at rt for 15 h. The mixture was filtered and the organic phase was washed with saturated $Na_2S_2O_3$ (5 mL), saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$) and the solvent was removed to give the title compound (**6**) as a yellow oil (0.853 g, 91%). IR (film): 3048, 2956, 2929, 2887, 2857 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.61−4.54 (m, 1H), 3.88 (ddd, *J* = 6.5, 6.4, 4.2 Hz, 0.4H), 3.49 (ddd, *J* = 8.7, 7.0, 4.5 Hz, 0.6H), 3.00−2.92 (m, 1H), 2.83−2.76 (m, 0.6H), 2.70−2.64 (m, 0.8H), 2.56 (dd, *J* = 4.9, 2.7 Hz, 0.6H), 2.02−1.80 (m, 2H), 0.92−0.90 (m, 18H), 0.16−0.08 (m, 21H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 106.8, 106.7, 90.1, 90.0, 72.7, 68.4, 61.2, 61.1, 56.0, 54.8, 45.2, 44.3, 43.7, 43.2, 26.0, 25.9, 18.4, 18.3, 0.0, −0.1, −4.2, −4.4, −4.5, −4.8, −4.9, −5.1. HRMS (ESI): *m/z* calcd for $C_{22}H_{47}O_3Si_3^+$ [M + H]$^+$ 443.2828; found 443.2827.

(1*S*,3*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-1-(oxiran-2-yl)-pent-4-yne (4b). A solution of **7b** (2.260 g, 6.37 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to a suspension of *m*-CPBA (77%, 3.180 g, 19.12 mmol) in anhydrous CH_2Cl_2 (25 mL) at rt under N_2 and the mixture was stirred at rt for 15 h. The mixture was filtered and the organic phase was washed with saturated $Na_2S_2O_3$ (10 mL), saturated $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$) and the solvent was removed to give an oily residue that was purified by flash chromatography [silica gel, hexanes−AcOEt, from 90:10 to 50:50 (gradient elution)] to give the title compound (**4b**)[12] as a pale yellow oil (2.240 g, 95%). IR (film): 3311, 3045, 2954, 2928, 2886, 2857 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.58 (m, 1H), 3.83 (dd, *J* = 7.8, 4.7 Hz, 0.4H), 3.49 (ddd, *J* = 8.7, 6.9, 4.3 Hz, 0.6H), 2.97 (ddd, *J* = 6.9, 4.1, 2.7 Hz, 0.6H), 2.93 (ddd, *J* = 4.5, 3.9, 2.7 Hz, 0.4H), 2.79 (dd, *J* = 4.8, 4.2 Hz, 0.6H), 2.72−2.64 (m, 0.8H), 2.57 (dd, *J* = 4.9, 2.7 Hz, 0.6H), 2.43 (d, *J* = 2.1 Hz, 0.4H), 2.41 (d, *J* = 2.1 Hz, 0.6H), 2.06−1.79 (m, 2H), 0.92−0.88 (m, 18H), 0.16−0.06 (m, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 85.0, 84.9, 73.3, 73.3, 72.4, 68.6, 60.5, 56.0, 54.7, 45.1, 44.7, 44.1, 43.5, 26.1, 26.0, 25.9, 18.4, 18.3, 18.2, −4.2, −4.5, −4.9, −5.0, −5.1. HRMS (ESI): *m/z* calcd for $C_{19}H_{39}O_3Si_2^+$ [M + H]$^+$ 371.2432; found 371.2425.

(1*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-(oxiran-2-yl)pent-4-yn-1-ol (4c). A suspension of *m*-CPBA (77%, 13.640 g, 60.83 mmol) in anhydrous CH_2Cl_2 (30 mL) at rt under N_2 was added to a stirred solution of **7c** (5.849 g, 24.33 mmol) in anhydrous CH_2Cl_2 (20 mL) and the mixture was stirred at rt for 15 h. The mixture was filtered and the organic phase was washed with saturated $Na_2S_2O_3$ (35 mL), saturated $NaHCO_3$ (2 × 15 mL), dried ($MgSO_4$) and the solvent was removed to give the title compound (**4c**)[9a] as a yellow oil (6.048 g, 97%). IR (film): 3454, 3318, 3083, 2962, 2930, 2895, 2860 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.58−4.54 (m, 1H), 3.89−3.83 (m, 0.4H), 3.72−3.65 (m, 0.6 H), 2.95 (ddd, *J* = 8.0, 4.1, 2.0 Hz, 1H), 2.71−2.63 (m, 2H), 2.38 (d, *J* = 2.1 Hz, 0.4H), 2.47 (d, *J* = 2.1 Hz, 0.6H), 1.98−1.81 (m, 2H), 0.81 (s, 9H), 0.08 (s, 1.2H), 0.08 (s, 1.8H), 0.06 (s, 1.2H), 0.05 (s, 1.8H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 84.5, 84.4, 73.6, 73.5, 69.7, 68.2, 61.7, 61.3, 55.2, 54.3, 44.9, 44.4, 42.4, 41.9, 25.8, 18.2, 18.1, −4.3, −4.4, −5.0, −5.1. HRMS (ESI): *m/z* calcd for $C_{13}H_{25}O_3Si^+$ [M + H]$^+$ 257.1568; found 257.1559.

(1*S*,3*R*)-3-(*tert*-Butyldiphenylsilyloxy)-1-(oxiran-2-yl)pent-4-yn-1-ol (4d). A suspension of *m*-CPBA (77%, 0.516 g, 2.26 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt under N_2 was added to a stirred solution of **7d** (0.275 g, 0.754 mmol) in anhydrous CH_2Cl_2 (2 mL) and the mixture was stirred at rt for 2.5 h. After filtration the organic phase was washed with saturated $Na_2S_2O_3$ (5 mL), saturated $NaHCO_3$ (2 × 15 mL) and dried ($MgSO_4$). Solvent removal gave the title compound (**4d**) as a pale yellow oil (0.290 g, 99%). IR (film): 3447, 3287, 2960, 2930, 2891, 2857, 2117 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77−7.66 (m, 4H), 7.47−7.35 (m, 6H), 4.67−4.59 (m, 1H), 4.10−4.04 (m, 0.4H), 3.84−3.76 (s, 0.6H), 3.05 (dd, *J* = 6.6, 3.7 Hz, 0.4H), 2.98 (td, *J* = 4.3, 2.8 Hz, 0.6H), 2.79−2.68 (m, 2H), 2.37 (d, *J* = 2.1 Hz, 1H), 2.02−1.85 (m, 3H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 136.2, 136.1, 135.9, 133.2, 133.2, 133.2, 130.10, 130.1, 130.0, 127.9, 127.8, 127.6, 127.5, 84.1, 84.1, 74.3, 74.2, 68.8, 66.7, 61.9, 61.7, 55.2, 54.4, 45.0, 43.9, 42.7, 41.7, 27.0, 19.4. HRMS (ESI): *m/z* calcd for $C_{23}H_{28}NaO_3Si^+$ [M + Na]$^+$ 403.1700; found 403.1702.

(1*S*,3*R*)-1-(Oxiran-2-yl)-3-(triisopropylsilyloxy)pent-4-yn-1-ol (4e). A solution of **7e** (4.900 g, 17.34 mmol) in anhydrous CH_2Cl_2 (7 mL) was added to a suspension of *m*-CPBA (77%, 9.500 g, 42.48 mmol) in anhydrous CH_2Cl_2 (33 mL) at rt under N_2 and the mixture was stirred at rt for 15 h. After filtration the organic phase was washed with saturated $Na_2S_2O_3$ (20 mL), saturated $NaHCO_3$ (2 × 20 mL) and dried ($MgSO_4$). Solvent removal gave the title compound (**4e**)[9a] as a pale yellow oil (4.920 g, 95%). IR (film): 3447, 3310, 2944, 2867, 2109 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.80−4.74 (m, 1H), 4.09−4.02 (m, 0.4H), 3.87−3.79 (m, 0.6H), 3.11−3.04 (m, 1H), 2.84−2.79 (m, 1H), 2.78−2.74 (m, 1H), 2.49 (d, *J* = 2.1 Hz, 0.4H), 2.47 (d, *J* = 2.1 Hz, 0.6H), 2.10−1.91 (m, 2H), 1.13−1.04 (m, 21H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 84.7, 84.6, 73.6, 73.6, 69.5, 67.5, 61.5, 61.2, 55.4, 54.4, 45.0, 44.2, 42.8, 42.1, 18.1, 18.1, 12.4, 12.3. HRMS (ESI): *m/z* calcd for $C_{16}H_{31}O_3Si^+$ [M + H]$^+$ 299.2037; found 299.2035.

(3*R*,5*S*)-5-Hydroxy-5-(oxiran-2-yl)pent-1-yn-3-yl Benzoate (4f). A solution of **7f** (0.500 g, 2.17 mmol, 91:9 mixture of monobenzoylated regioisomers) in anhydrous CH_2Cl_2 (3 mL) was added to a suspension of *m*-CPBA (77%, 1.460 g, 6.51 mmol) in anhydrous CH_2Cl_2 (2 mL) at rt under N_2 and the mixture was stirred at rt for 15 h. After filtration the organic phase was washed with saturated $Na_2S_2O_3$ (7 mL), saturated $NaHCO_3$ (2 × 10 mL) and dried ($MgSO_4$). Solvent removal gave an oily residue that was purified by flash chromatography [silica gel, hexanes−AcOEt, from 90:10 to 50:50 (gradient elution)] to give the title compound (**4f**) as a pale yellow oil (0.465 g, 87%, single monobenzoylated regioisomer). IR (film): 3446, 3288, 3063, 2997, 2929, 2121, 1719 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07−8.01 (m, 2H), 7.60−7.53 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 5.89−5.81 (m, 1H), 4.18 (ddd, *J* = 7.9, 4.8, 3.3 Hz, 0.4H), 3.86 (dt, *J* = 9.0, 4.6 Hz, 0.6H), 3.09 (ddd, *J* = 7.4, 6.0, 2.9 Hz, 1H), 2.88−2.81 (m, 1H), 2.79−2.74 (m, 0.6H), 2.72 (dd, *J* = 5.0, 4.0 Hz, 0.4H), 2.56 (t, *J* = 1.9 Hz, 1H), 2.32−2.13 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.4, 133.5, 133.4, 129.9, 129.9, 129.6, 129.6, 128.6, 128.5, 80.7, 80.6, 74.9, 74.8, 68.5, 65.9, 62.1, 62.0, 55.1, 54.2, 45.1, 43.7, 39.3, 38.4. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}O_4^+$ $[M + H]^+$ 247.0965; found 247.0966.

(1*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-(oxiran-2-yl)pent-4-ynyl Acetate (4g). NEt_3 (3.80 mL, 27.89 mmol) was added dropwise to a solution of **4c** (5.499 g, 21.45 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (50 mL) at 0 °C under N_2. Ac_2O (2.40 mL, 25.74 mmol) was added dropwise at 0−5 °C and the mixture was allowed to warm to rt and stirred for 1 h. Saturated NH_4Cl (35 mL) was added slowly and the mixture was stirred for 10 min. After partitioning the aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic phases were washed with saturated $NaHCO_3$ (30 mL). The aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic phases were dried ($MgSO_4$) and the solvent was removed to give the title compound[9a] (**4g**) as a pale yellow oil (6.300 g, 98%). IR (film): 3295, 3075, 2970, 2947, 2903, 2873, 1750 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.07−4.99 (m, 1H), 4.54−4.48 (m, 1H), 3.16 (ddd, *J* = 5.7, 4.1, 2.6 Hz, 0.6H), 3.05 (ddd, *J* = 4.9, 3.9, 2.7 Hz, 0.4H), 2.82 (dd, *J* = 4.9, 4.2 Hz, 0.6H), 2.77−2.70 (m, 0.8H), 2.67 (dd, *J* = 4.8, 2.7 Hz, 0.6H), 2.44 (d, *J* = 2.1 Hz, 0.6H), 2.43 (d, *J* = 2.1 Hz, 0.4H), 2.08 (s, 1.2H), 2.06 (s, 1.8H), 2.16−1.97 (m, 2H), 0.90 (s, 9H), 0.15 (s, 1.8H), 0.14 (s, 1.2H), 0.12 (s, 1.8H), 0.12 (s, 1.2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.1, 85.1, 74.5, 74.4, 72.0, 70.9, 60.8, 54.1, 53.2, 46.3, 40.9, 40.7, 26.8, 22.1, 22.0, 19.2, −3.5, −4.1. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{27}O_4Si^+$ $[M + H]^+$ 299.1674; found 299.1665.

(5*R*,7*S*)-5-Ethynyl-2,2,3,3,10,10-hexamethyl-7-(oxiran-2-yl)-9,9-diphenyl-4,8-dioxa-3,9-disilaundecane (4h). TBDPSCl (0.17 mL, 0.66 mmol) was added dropwise to a solution of **4c** (0.085 g, 0.33 mmol) and imidazole (0.050 g, 0.73 mmol) in anhydrous THF (3 mL) at 0 °C under N_2, and the mixture was warmed to 30 °C and stirred for 48 h. A 22% solution of NH_4Cl (5 mL) was added slowly and the mixture was stirred for 10 min. MTBE (15 mL) and H_2O (5 mL) were added and the mixture was stirred for 10 min and partitioned. The organic phase was dried ($MgSO_4$), and the solvent was removed. The resulting oily residue was purified by flash chromatography (silica gel, hexanes−AcOEt 98:2) to give the title compound (**4h**) as a colorless oil (0.130 g, 79%). IR (film): 3309, 3049, 2956, 2930, 2892, 2857 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73−7.68 (m, 4H), 7.44−7.32 (m, 6H), 4.70 (ddd, *J* = 7.6, 6.9, 2.1 Hz, 0.4H), 4.57 (dt, *J* = 6.8, 2.1 Hz, 0.6H), 3.69−3.57 (m, 1H), 3.11−3.04 (m, 0.6H), 2.90−2.84 (m, 0.4H), 2.67 (dd, *J* = 4.8, 4.3 Hz, 0.6H), 2.46 (dd, *J* = 4.9, 2.7 Hz, 0.6H), 2.32−2.28 (m, 0.6H), 2.20 (d, *J* = 2.1 Hz, 0.4H), 1.99 (m, 1H), 1.91−1.82 (m, 1H), 1.08 (s, 9H), 0.85 (s, 9H), 0.12 (s, 0.6H), 0.09 (s, 2.4H), 0.07 (s, 0.6H), 0.07 (s, 2.4H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 136.2, 136.1, 136.1, 136.0, 134.0, 133.8, 133.7, 133.4, 130.0, 129.9, 129.8, 129.7, 127.8, 127.7, 127.7, 127.5, 85.1, 84.7, 73.1, 73.0, 72.9, 71.3, 60.1, 60.0, 55.6, 54.5, 46.5, 45.2, 44.6, 43.5, 27.2, 27.1, 25.9, 25.8, 19.6, 19.5, 18.3, 18.2, −4.4, −4.5, −4.9. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{46}NO_3Si_2^+$ $[M + NH_4]^+$ 512.3011; found 512.3005.

(5*R*,7*S*)-5-Ethynyl-2,2,9,9,10,10-hexamethyl-7-(oxiran-2-yl)-3,3-diphenyl-4,8-dioxa-3,9-disilaundecane (4i). A solution of TBSCl (0.230 g, 1.53 mmol) in anhydrous THF (2 mL) was added dropwise to a solution of **4d** (0.220 g, 0.58 mmol) and imidazole (0.110 g, 1.62 mmol) in anhydrous THF (3 mL) at 0 °C under N_2, and the mixture was warmed to 30 °C and stirred for 24 h. A 22% solution of NH_4Cl (5 mL) was added slowly and the mixture was stirred for 10 min. MTBE (15 mL) and H_2O (5 mL) were added and the mixture was stirred for 10 min and partitioned. The organic phase was dried ($MgSO_4$), and the solvent was removed. The resulting oily residue was purified by flash chromatography [silica gel, hexanes−AcOEt, from 99:1 to 90:10 (gradient elution)] to give the title compound (**4i**) as a colorless oil (0.203 g, 71%). IR (film): 3307, 3071, 2955, 2928, 2892, 2856 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.89−7.78 (m, 4H), 7.60−7.46 (m, 6H), 4.71−4.62 (m, 1H), 3.93 (dt, *J* = 8.0, 4.1 Hz, 0.3H), 3.64−3.54 (m, 0.7H), 3.07−2.96 (m, 1H), 2.88 (dd, *J* = 4.8, 4.2 Hz, 0.7H), 2.80 (dd, *J* = 5.4, 4.2 Hz, 0.3H), 2.74 (dd, *J* = 5.4, 2.8 Hz, 0.3H), 2.66 (dd, *J* = 4.9, 2.8 Hz, 0.7H), 2.50 (d, *J* = 2.1 Hz, 0.3H), 2.48 (d, *J* = 2.1 Hz, 0.7H), 2.20−2.00 (m, 2H), 1.22 (bs, 9H), 0.87 (bs, 6H), 0.84 (s, 3H), 0.19 (s, 2H), 0.14 (s, 1H), 0.11 (s, 1H), 0.04 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 136.2, 136.1, 135.9, 135.9, 133.5, 133.4, 130.0, 129.9, 129.8, 129.7, 127.8, 127.8, 127.6, 127.5, 84.5, 84.4, 74.1, 74.0, 72.4, 68.6, 61.8, 56.0, 54.7, 45.0, 44.7, 43.6, 43.0, 27.0, 25.9, 25.9, 19.4, 18.1, 18.1, −4.4, −4.3, −5.1, −5.3. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{42}NaO_3Si_2^+$ $[M + Na]^+$ 517.2565; found 517.2572.

(1*S*,3*R*)-1-(Oxiran-2-yl)-3-(triisopropylsilyloxy)pent-4-yn-1-yl Acetate (4j). NEt_3 (0.29 mL, 2.15 mmol) was added dropwise to a solution of **4e** (0.495 g, 1.66 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (5 mL) at 0 °C under N_2. Ac_2O (0.19 mL, 1.99 mmol) was added dropwise at 0 °C and the mixture was allowed to warm to rt and stirred for 1 h. Saturated NH_4Cl (5 mL) was added slowly and the mixture was stirred for 10 min. After partitioning the aqueous phase was extracted with CH_2Cl_2 (5 mL) and the organic phases were combined and washed with saturated $NaHCO_3$ (2 × 5 mL). The combined organic phases were dried ($MgSO_4$), and solvent removal gave the title compound (**4j**) as a yellow oil (0.508 g, 90%). IR (film): 3301, 3064, 2944, 2867, 2118 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.12−5.06 (m, 1H), 4.64−4.55 (m, 1H), 3.17 (ddd, *J* = 5.6, 4.2, 2.7 Hz, 0.6H), 3.07 (ddd, *J* = 4.4, 3.7, 2.6 Hz, 0.4H), 2.83 (dd, *J* = 4.9, 4.2 Hz, 0.6H), 2.75 (m, 0.8H), 2.68 (dd, *J* = 4.9, 2.6 Hz, 0.6H), 2.44 (m, 1H), 2.15−1.99 (m, 5H), 1.18−0.98 (m, 21H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.1, 84.1, 73.5, 73.4, 70.9, 69.8, 60.0, 59.9, 53.2, 52.2, 45.3, 40.2, 39.7, 21.0, 20.9, 18.1, 18.0, 17.8, 12.4, 12.3, 12.2. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{33}O_4Si^+$ $[M + H]^+$ 341.2143; found 341.2141.

(3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-5-(oxiran-2-yl)pent-1-yn-3-yl Benzoate (4k). A solution of TBSCl (0.464 g, 3.08 mmol) in anhydrous THF (2 mL) was added dropwise to a solution of **4f** (0.400 g, 1.62 mmol) and imidazole (0.330 g, 4.86 mmol) in anhydrous THF (3 mL) at 0 °C under N_2, and the mixture was warmed to 30 °C and stirred for 24 h. A 22% solution of NH_4Cl (5 mL) was added slowly and the mixture was stirred for 10 min. MTBE (15 mL) and H_2O (5 mL) were added and the mixture was stirred for 10 min and partitioned. The organic phase was dried ($MgSO_4$), and the solvent was removed. The resulting oily residue was purified by flash chromatography [silica gel, hexanes−AcOEt, from 95:5 to 90:10 (gradient elution)] to give the title compound (**4k**) as a white waxy solid (0.390 g, 67%). IR (film): 3270, 3066, 2954, 2928, 2886, 2856, 2121, 1724 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.09−8.03 (m, 2H), 7.62−7.53 (m, 1H), 7.48−7.41 (m, 2H), 5.83−5.75 (m, 1H), 3.90 (dt, *J* = 7.4, 4.6 Hz, 0.3H), 3.60 (ddd, *J* = 8.7, 6.8, 4.4 Hz, 0.7H), 3.02−2.80 (m, 1H), 2.70−2.66 (m, 0.6H), 2.53 (m, 1.4H), 2.29−2.18 (m, 1H), 2.14−2.03 (m, 1H), 0.93 (bs, 9H), 0.16 (s, 1.5H), 0.14 (s, 3H), 0.09 (s, 1.5H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.3, 165.2, 133.4, 133.4, 129.9, 129.8, 129.7, 128.6, 128.5, 80.8, 74.8, 74.7, 72.0, 68.6, 62.1, 61.8, 55.7, 54.5, 45.2, 45.0, 40.1, 39.6, 26.0, 25.9, 18.2, −4.2, −4.3, −4.9, −5.1. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{32}NO_4Si^+$ $[M + NH_4]^+$ 378.2095; found 378.2099.

General Procedure for Noncatalytic 5-Exo Cyclization. Strictly deoxygenated anhydrous THF (76 mL) was added to a mixture of Cp_2TiCl_2 (1.711 g, 6.87 mmol) and activated Zn powder (1.800 g, 27.48 mmol) under N_2 and the suspension was stirred at rt until it turned lime green. This suspension was then added slowly to a solution of **4b** (0.850 g, 2.29 mmol) over 3 h and the mixture was stirred for 15 h at rt. A 22% solution of NH_4Cl (60 mL) was added slowly and the mixture was stirred for 2 h, filtered and the solvent was removed. AcOEt (100 mL) was added and the mixture was stirred for

10 min. The mixture was partitioned and the aqueous phase was extracted with AcOEt (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed. The resulting oily residue was purified by flash chromatography [silica gel, hexanes−AcOEt, from 95:5 to 80:20 (gradient elution)] to give the title compound as a pale yellow oil (0.424 g, 50%).

((1*R*,3*R*,5*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2-methylenecyclopentyl)methanol (5b).[12] $[\alpha]_D^{25}$ −30.4 (*c* 1.0, $CHCl_3$). IR (film): 3460, 3070, 2956, 2930, 2887, 2858 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.21 (t, *J* = 2.3 Hz, 1H), 5.01 (t, *J* = 2.3 Hz, 1H), 4.33 (ddd, *J* = 9.3, 4.8, 2.3 Hz, 1H), 4.00 (ddd, *J* = 10.1, 8.0, 6.2 Hz, 1H), 3.82−3.69 (m, 2H), 2.66−2.59 (m, 1H), 2.24 (dd, *J* = 11.6, 6.2 Hz, 1H), 1.67−1.61 (m, 1H), 0.92 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 6H), 0.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.1, 108.4, 72.4, 71.0, 63.0, 53.2, 43.9, 26.0, 25.9, 18.4, 18.1, −4.1, −4.4, −4.6, −4.7. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{41}O_3Si_2^+$ [M + H]$^+$ 373.2589; found 373.2592.

(1*S*,2*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-hydroxymethyl-3-methylenecyclopentyl acetate (5g).[9a] $[\alpha]_D^{25}$ −43.5 (*c* 1.0, $CHCl_3$). IR (film): 3462, 3083, 2955, 2930, 2887, 2858, 1734 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.24 (t, *J* = 2.3 Hz, 1H), 5.1 (t, *J* = 2.3 Hz, 1H), 4.99 (dt, *J* = 8.4, 6.4 Hz, 1H), 4.42 (m, 1H), 3.70 (d, *J* = 5.8 Hz, 2H), 2.84−2.73 (m, 1H), 2.48−2.38 (m, 1H), 2.07 (s, 3H), 1.81−1.69 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.9, 151.7, 109.0, 73.5, 72.7, 63.7, 51.0, 40.5, 25.9, 21.3, 18.3, −4.5, −4.7. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{29}O_4Si^+$ [M + H]$^+$ 301.1830; found 301.1816.

((1*R*,3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2-methylenecyclopentyl)methanol (5h). $[\alpha]_D^{25}$ −18.3 (*c* 1.0, $CHCl_3$). IR (ATR): 3454, 3070, 2955, 2929, 2888, 2856 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73−7.65 (m, 4H), 7.47−7.35 (m, 6H), 5.17 (t, *J* = 2.3 Hz, 1H), 4.99 (t, *J* = 2.3 Hz, 1H), 4.18−4.09 (m, 1H), 4.02 (dt, *J* = 9.5, 6.7 Hz, 1H), 3.60 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.49 (dd, *J* = 11.1, 4.5 Hz, 1H), 2.75−2.71 (m, 1H), 2.01−1.92 (m, 1H), 1.63 (dt, *J* = 11.4, 9.5 Hz, 1H), 1.06 (s, 9H), 0.86 (s, 9H), 0.00 (s, 3H), −0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.4, 136.0, 134.3, 134.0, 131.0, 130.0, 129.9, 128.0, 127.9, 127.8, 126.7, 108.2, 72.4, 71.6, 62.7, 53.6, 43.7, 27.1, 26.0, 19.3, 18.3, −4.5, −4.7. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{48}NO_3Si_2^+$ [M + NH_4]$^+$ 514.3167; found 514.3165.

(1*R*,3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxymethyl-2-methylenecyclopentyl Benzoate (5k). $[\alpha]_D^{25}$ −26.4 (*c* 1.0, $CHCl_3$). IR (ATR): 3503, 3064, 2954, 2929, 2885, 2856, 1718 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10−8.04 (m, 2H), 7.61−7.53 (m, 1H), 7.49−7.40 (m, 2H), 5.66−5.61 (m, 1H), 5.37 (t, *J* = 2.4 Hz, 1H), 5.19 (t, *J* = 2.4 Hz, 1H), 4.19−4.10 (m, 1H), 3.86−3.80 (m, 2H), 2.81−2.71 (m, 1H), 2.64−2.55 (m, 1H), 1.83 (dt, *J* = 12.7, 8.4 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.5, 147.7, 133.1, 130.3, 129.8, 128.5, 112.0, 74.2, 72.2, 62.5, 53.5, 40.5, 25.9, 18.0, −4.3, −4.8. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{31}O_4Si^+$ [M + H]$^+$ 363.1986; found 363.1988.

Catalytic 5-Exo Cyclization of 4g. Strictly deoxygenated anhydrous THF (15 mL) was added to a mixture of IrCl(CO)(PPh_3)$_2$ (0.260 g, 0.34 mmol) and manganese powder (0.368 g, 6.70 mmol). A solution of 2,4,6-collidine (3.5 mL, 26.8 mmol) and **4g** (1.000 g, 3.35 mmol) in strictly deoxygenated anhydrous THF (22 mL) was added at rt. TMSCl (1.7 mL, 13.4 mmol) was added followed by a solution of Cp_2TiCl_2 (0.167 g, 0.67 mmol) in strictly deoxygenated anhydrous THF (12 mL) and the mixture was stirred for 4 h under H_2 (4 bar) at rt. Water (5 mL) was added and the mixture was stirred for 10 min and filtered through Celite. The pad was washed with MTBE (20 mL) and the organic phases were combined and acidified to pH = 2 with 2 M HCl. The mixture was stirred for 15 min and the phases were separated. The organic phase was washed with H_2O (20 mL) and dried (Na_2SO_4). The solvent was removed and the resulting oily residue was purified by flash chromatography [silica gel, hexanes−AcOEt, from 90:10 to 60:40 (gradient elution)] to give the title compound (**5g**) as a pale yellow oil (0.582 g, 58%).

((1*R*,3*R*,5*S*)-5-Acetoxy-3-(*tert*-butyldimethylsilyloxy)-2-methylenecyclopentyl)methyl 4-Nitrobenzoate (5l). NEt_3 (0.65 mL, 4.62 mol) was added dropwise to a solution of **5g** (1.000 g, 3.33 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (9 mL) at 0 °C under N_2. A solution of *p*-nitrobenzoyl chloride (0.740 g, 3.99 mmol) in anhydrous CH_2Cl_2 (4 mL) was added dropwise at 0−5 °C. The mixture was allowed to warm to rt and was stirred for 2 h. Saturated NH_4Cl (10 mL) was added slowly and the mixture was stirred for 15 min. The mixture was partitioned and the organic phase was washed with H_2O and dried (Na_2SO_4). The solvent was removed and the resulting oily residue was purified by flash chromatography (silica gel, hexanes−AcOEt 90:10) to give the title compound (**5l**) as white solid (1.102 g, 74% yield). Mp 83 °C. $[\alpha]_D^{25}$ −8.6 (*c* 1.0, $CHCl_3$). IR (ATR): 2981, 2959, 2944, 2884, 2858, 1730, 1713 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31−8.13 (m, 4H), 5.27 (t, *J* = 2.3 Hz, 1H), 5.13 (t, *J* = 2.3 Hz, 1H), 5.05 (dt, *J* = 8.4, 6.6 Hz, 1H), 4.48 (m, 3H), 3.18−3.08 (m, 1H), 2.59−2.44 (m, 1H), 1.99 (s, 3H), 1.79−1.64 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.9, 164.6, 150.7, 150.5, 135.5, 130.8, 123.7, 110.1, 73.2, 72.5, 66.3, 46.9, 40.5, 25.9, 21.2, 18.3, −4.5, −4.6. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{32}NO_7Si^+$ [M + H]$^+$ 450.1943; found 450.1947.

((1*R*,3*R*,5*S*)-5-Acetoxy-3-hydroxy-2-methylenecyclopentyl)methyl 4-Nitrobenzoate (5m). (+)-Camphorsulfonic acid ((+)-CSA, 0.034 g, 0.15 mmol) was added to a solution of **5l** (0.660 g, 1.47 mmol) in anhydrous MeOH (7 mL) at rt under N_2. The mixture was stirred for 2 h and was then cooled to 0 °C and stirred for 1 h. The pH was adjusted to 6.5 by adding 1% $NaHCO_3$ solution. The MeOH was removed in *vacuo* and the aqueous layer was extracted with MTBE. The organic phase was dried (Na_2SO_4), the solvent was removed and the resulting oily residue was purified by flash chromatography (silica gel, hexanes−AcOEt 60:40) to give the title compound (**5m**) as a white solid (0.439 g, 89%). Mp 73 °C. $[\alpha]_D^{25}$ −32.7 (*c* 1.0, $CHCl_3$). IR (KBr): 3460, 3109, 3074, 3050, 2990, 2927, 1722 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26−8.22 (m, 4H), 5.44 (bs, 1H), 5.25 (d, *J* = 1.5 Hz, 1H), 5.17 (q, *J* = 5.5 Hz, 1H), 4.56−4.54 (m, 1H), 4.52−4.43 (m, 1H), 4.42−4.30 (m, 1H), 3.21−3.18 (m, 1H), 2.53−2.49 (m, 1H), 2.02 (s, 3H), 1.85 (dt, *J* = 12.4, 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.6, 164.6, 151.3, 150.8, 135.4, 130.8, 123.8, 112.3, 74.8, 73.2, 65.9, 47.9, 40.1, 21.3. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_2O_7^+$ [M + NH_4]$^+$ 353.1343; found 353.1328.

((1*R*,3*S*,5*S*)-5-Acetoxy-3-(2-amino-6-chloro-9*H*-purin-9-yl)-2-methylenecyclopentyl)methyl 4-Nitrobenzoate (13). A mixture of 2-amino-6-chloropurine (7.380 g, 43.54 mmol) and triphenylphosphine (11.400 g, 43.54 mmol) in anhydrous THF (927 mL) at rt under N_2 was stirred for 15 min. After cooling to −10 °C, diisopropyl azodicarboxylate (DIAD, 8.60 mL, 43.54 mmol) was added dropwise and the mixture was stirred for 10 min. A solution of **5m** (7.300 g, 21.77 mmol) in anhydrous THF (160 mL) was added over 1 h. The mixture was stirred for 3 h at −10 °C and was then allowed to warm to rt, filtered and the residue was washed with THF (109 mL). The solvent was removed and the resulting oily residue was purified by crystallization from isopropanol (440 mL) to afford the title compound as a pale yellow solid (6.510 g, 61%). Mp 113 °C. $[\alpha]_D^{25}$ +9.8 (*c* 1.0, $CHCl_3$). IR (KBr): 3498, 3382, 3213, 3082, 2970, 1728, 1715 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (dd, *J* = 20.6, 8.9 Hz, 4H), 7.80 (s, 1H), 5.58−5.40 (m, 2H), 5.35−5.30 (m, 1H), 4.91 (bs, 1H), 4.85 (dd, *J* = 11.4, 9.3 Hz, 1H), 4.62 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.28−3.24 (m, 1H), 2.85 (ddd, *J* = 14.3, 10.6, 5.2 Hz, 1H), 2.42 (dd, *J* = 14.3, 8.1 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.3, 165.0, 158.9, 153.1, 151.8, 150.8, 146.2, 141.9, 135.2, 130.9, 125.9, 123.8, 113.6, 74.6, 65.9, 57.4, 48.7, 35.5, 21.3. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{20}ClN_6O_6^+$ [M + H]$^+$ 487.1127; found 487.1132.

((1*R*,3*S*,5*S*)-5-Acetoxy-3-(2-amino-6-oxo-1*H*-purin-9(6*H*)-yl)-2-methylenecyclopentyl)methyl 4-Nitrobenzoate (14). A solution of **13** (6.300 g, 12.94 mmol) in formic acid 80% (126 mL) at 50 °C under N_2 was stirred for 9 h. The solvent was removed, H_2O (72 mL) was added and the suspension was stirred for 18 h at rt. The suspension was filtered and the solid was dried to afford the title compound (**14**) as a yellow solid (5.590 g, 92%). Mp 282 °C. $[\alpha]_D^{25}$ +2.9 (*c* 1.0, DMSO). IR (KBr): 3408, 3315, 3210, 3110, 2934, 2868, 1728, 1706 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.08 (bs, 1H), 8.37 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H), 7.74 (s, 1H), 6.66 (bs, 2H), 5.42−5.35 (m, 1H), 5.35−5.31 (m, 1H), 5.27 (bs, 1H), 4.67 (bs, 1H), 4.59−4.55 (m, 2H), 3.17−3.10 (m, 1H), 2.70 (ddd, J = 13.6, 11.3, 5.3 Hz, 1H), 2.34−2.25 (m, 1H), 2.01 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 169.9, 164.3, 156.8, 153.5, 151.2, 150.3, 147.8, 136.1, 135.1, 130.7, 123.9, 116.5, 111.2, 74.1, 65.6, 55.2, 47.8, 35.2, 21.0. HRMS (ESI): m/z calcd for $C_{21}H_{21}N_6O_7^+$ [M + H]$^+$ 469.1466; found 469.1461.

2-Amino-9-((1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl)-1*H*-purin-6(9*H*)-one Monohydrate (1). A solution of MeONa (30%, 4.10 mL, 22.20 mmol) was added dropwise to a solution of **14** (5.200 g, 11.10 mmol) in anhydrous MeOH (40 mL) at rt under N_2. The mixture was stirred for 30 min at rt and cooled to 0 °C. MTBE (52 mL) was added and the mixture was neutralized (pH = 7) with HCl. The phases were separated and the aqueous layer was extracted with MTBE (50 mL). The volume of the aqueous phase was reduced to 45 mL by distillation. The suspension was heated at 85 °C and was slowly cooled to rt and stirred for 15 h. After filtration the isolated solid was dried under vacuum to afford the title compound (**1**) as a white solid with a 6.5% water content (as determined by Karl Fischer titration) and 98.8% HPLC purity (2.370 g, 72% yield). This white solid **1**[5a] was recrystallized from water to afford **1** (2.102 g, 64% overall yield, 99.47% HPLC purity) with a 6.7% water content (as determined by Karl Fischer titration). Mp 248 °C. $[\alpha]_D^{25}$ +35.0 (c 0.4, H_2O). IR (ATR): 3445, 3361, 3296, 3175, 3113, 2951, 2858, 2626, 1709 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.59 (s, 1H), 7.66 (s, 1H), 6.42 (bs, 2H), 5.36 (ddt, J = 10.6, 7.8, 2.7 Hz, 1H), 5.10 (dd, J = 2.7, 2.2 Hz, 1H), 4.87 (d, J = 3.1 Hz, 1H), 4.84 (t, J = 5.3 Hz, 1H), 4.56 (t, J = 2.4 Hz, 1H), 4.23 (m, 1H), 3.53 (m, 2H), 2.52 (m, 1H), 2.22 (ddd, J = 12.6, 10.8, 4.6 Hz, 1H), 2.04 (ddt, J = 12.6, 7.7, 1.9 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 156.9, 153.5, 151.5, 151.3, 136.0, 116.2, 109.3, 70.4, 63.1, 55.2, 54.1, 39.2. HRMS (ESI): m/z calcd for $C_{12}H_{16}N_5O_3^+$ [M + H]$^+$ 278.1253; found 278.1262.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of **1**, **3a-e**, **4b−k**, **5b**, **5g−h**, **5k−m**, **6**, **7a−f**, **13** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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