CHEMISTRY
AN ASIAN JOURNAL
ACES
FULL PAPER

DOI: 10.1002/asia.201301647

Total Synthesis of the Putative Structure of Xylarinol B

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Abstract: The total synthesis of the putative structure of xylarinol B is described and the need to revise its structure is demonstrated. The central benzoxepine skeleton was constructed by employing a cobalt-mediated bimolecular [2+2+2] Reppe–Vollhardt alkyne cycloaddition reaction.

Keywords: chiral pool · cobalt · natural products · structure elucidation · total synthesis

Introduction

In 2009, the group of Yun isolated two 2-benzoxepine derivatives from the fruiting bodies of the *Xylaria polymorpha* species and named them xylarinols A (**1**) and B (**2**) (Figure 1).[1] The 2-benzoxepine unit of xylarinols is a rare structural moiety present in natural products.[2] There are

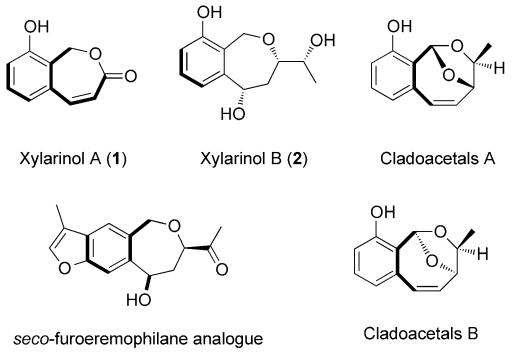
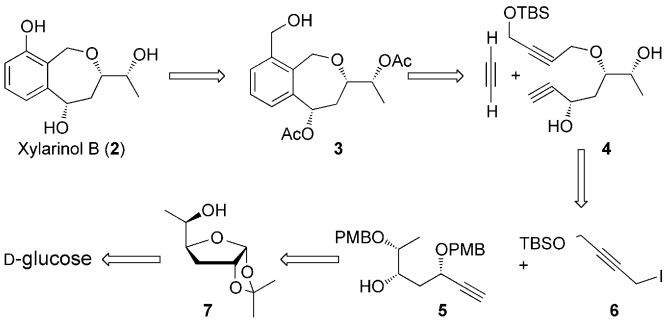


Figure 1. Some natural products with the 2-benzoxepin core.

several methods for the synthesis of the 2-benzoxepine unit.[3] However, reports on the total synthesis of related natural products are limited. Recently, Hsu and Lin reported the synthesis of cladoacetals A and B, which are closely related to **2**.[4] Starting with a suitably functionalized benzene derivative, a Suzuki coupling followed by an acid-catalyzed intramolecular acetalization have been employed as the key steps for the oxepine ring annulation. The synthesis of benzo-fused compounds through metal-catalyzed [2+2+2] cyclotrimerization of triynes is an important method that addresses the construction of polycyclic systems in one step with complete atom economy.[5–7] More importantly, when the cyclotrimerization is intermolecular in nature, it provides an easy access to the structural variants of the targeted molecules without any deviation from the original route. The synthesis of the benzoxepine unit employing the intramolecular [2+2+2] cyclotrimerization has been well documented.[7] Nonetheless, the intermolecular version has not yet been documented. This prompted us to explore the possibility of constructing the complete 2-benzoxepine skeleton by employing the [2+2+2] cyclotrimerization reaction of a linear diyne.

Results and Discussion

The salient features of our retrosynthetic disconnections for **2** are depicted in Scheme 1. The installation of the phenolic hydroxy group has been identified as the final step in the total synthesis. This has been planned through the oxidation



Scheme 1. Retrosynthetic strategy for the xylarinol B (**2**). TBS = *tert*-butyldimethylsilyl ether, PMB = *p*-methoxylbenzyl ether.

of benzyl alcohol **3** and the Dakin oxidation of the resulting benzaldehyde derivative. Keeping the [2+2+2] cyclotrimerization reaction as a key step, the penultimate intermediate **3** could be assembled from diyne **4** and acetylene. One of the alkyne components in diyne **4** was planned through O-alkylation of **5** with propargyl iodide derivative **6**, while the other alkyne could be accessed from the Ohira–Bestmann

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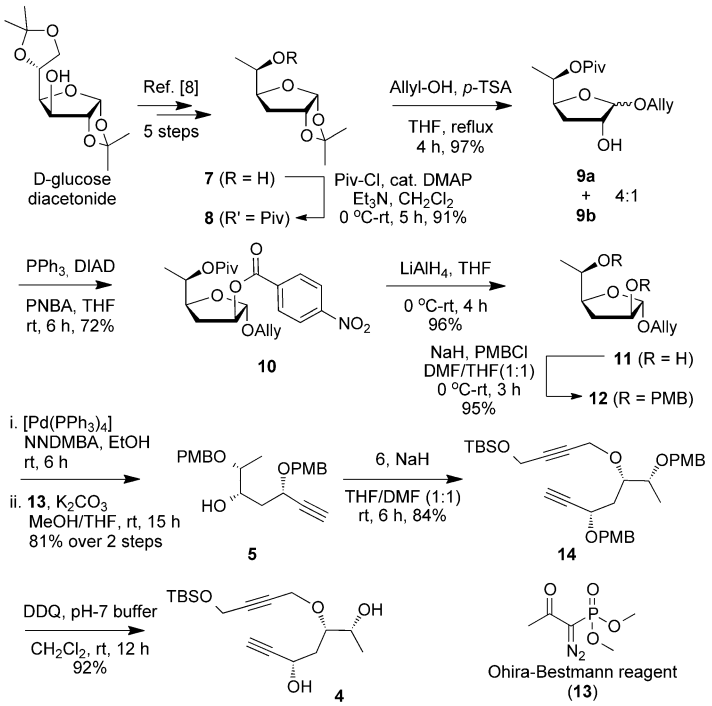
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201301647.



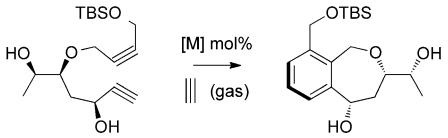
Scheme 2. Synthesis of key intermediate **4**. *p*-TSA = *para*-toluenesulfonic acid, Piv-Cl = pivaloyl chloride, DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran, DIAD = diisopropyl azodicarboxylate, PNBA = *para*-nitrobenzoic acid, DMF = *N*,*N*-dimethylformamide, NNDMBA = 1,3-dimethylbarbituric acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

alkynylation of a suitably protected lactal derived from **7**, which was identified as the key starting precursor.

The synthetic procedure began with **7** (Scheme 2), which was prepared from D-glucose diacetonide in five steps.[8] The protection of the free −OH group as its pivaloate ester followed by acetonide hydrolysis of resulting compound **8** in the presence of allylic alcohol and catalytic p-TSA led to the formation of an anomeric mixture of allylribofuranosides **9** (α/β, 4:1). The major **9**α anomer was subjected to the Mitsunobu reaction to invert the configuration of C(2)−OH. Subsequently, saponification of the resulting benzoate derivative **10** gave diol **11**. The two free hydroxyl groups in compound **11** were protected as their *p*-anisyl ethers. Palladium-catalyzed one-pot olefin isomerization and allyl transfer to a nucleophilic allyl scavenger[9] of the resulting dianisyl ether derivative **12** followed by Ohira–Bestmann alkynylation[10] of the intermediate lactal gave the corresponding key alkynol **5** in good yields. With alkynol **5** in hand, our next concern was the synthesis of diyne **4** and its cyclotrimerization with acetylene. To this end, treatment of alkynol **5** with propargyl iodide (**6**)[11] provided diyne **14** in 84% yield. Key cyclotrimerization substrate **4** was prepared by selective removal of the *p*-anisyl ether group by using DDQ in a suspension of pH 7 buffer/dichloromethane.

The cyclotrimerization of diyne **4** with acetylene needed substantial optimization (Table 1). The reaction with the $[RhCl(PPh_3)_3]$ catalyst (5 mol%) in toluene at 80°C was

Table 1. Optimization of the [2+2+2] cyclotrimerization of the diyne **4** with acetylene.[a]



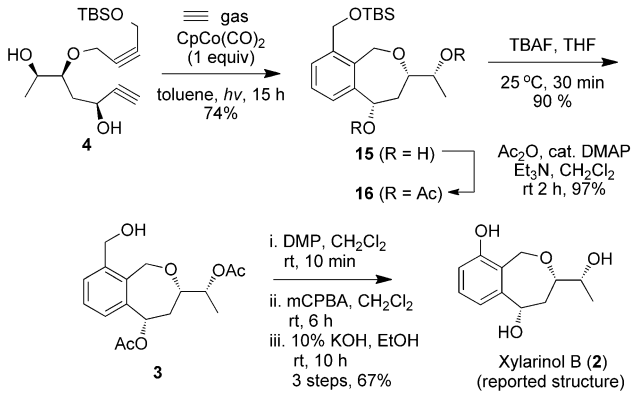
1,8-diyne (**4**) (**15**)

	Catalyst	Equiv	Solvent	T[b] [°C]	t [h]	Yield[c] [%]
1	$[RhCl(PPh_3)_3]$	0.05	$PhCH_3$	80	6	≈10
2	$[RhCl(PPh_3)_3]$	0.05	$PhCH_3$	μw	6	–
3	[RuCl(cod)Cp*]	0.05	DCE	80	15	–
4	[RuCl(cod)Cp*]	0.05	CH_2Cl_2	25	15	–
5	$[Co(CO)_2Cp]$	0.10	DCE	80	6	≈10
6	$[Co(CO)_2Cp]$[d]	0.10	$PhCH_3$	80	8	≈10
7	$[Co(CO)_2Cp]$	0.10	$PhCH_3$	μw	8	≈10
8	$[Co(CO)_2Cp]$	0.50	$PhCH_3$	*hv*	15	32
9	$[Co(CO)_2Cp]$	1	$PhCH_3$	*hv*	15	74

[a] Cp = cyclopentadienyl, Cp* = pentamethylcyclopentadienyl, COD = cyclooctadienyl, DCE = 1,2-dichloroethane. [b] *hv* = 200 W, the bulb was kept 2 cm away from the sealed tube (approx. 115°C); μw = microwave irradiation (150°C). [c] Yields of product isolated. [d] 10 mol% PPh_3 was added.

sluggish, with less than 10% conversion (Table 1, entry 1) of the diyne **4**. Changing from conventional heating to microwave heating (Table 1, entry 2) did not lead to any improvement. Similarly, [RuCl(cod)Cp*] was found to be ineffective in either of the solvents employed, DCE or CH_2Cl_2 (Table 1, entries 3 and 4, respectively). If $[Co(CO)_2Cp]$ was employed as the catalyst[12] (10 mol%), the formation of the desired product was observed. However, the yield was poor (Table 1, entry 5). Neither the addition of PPh_3 (10 mol%), (Table 1, entry 6)[12] nor microwave irradiation (Table 1, entry 7) improved the product yields.[7p] However, enhanced conversion (32%) along with unreacted starting material and undesired dimerized products were observed under irradiation if 50 mol% $[Co(CO)_2Cp]$ in toluene was employed (Table 1, entry 8).[12f] Eventually, the use of $[Co(CO)_2Cp]$ (1 equiv) in a sealed tube under conventional irradiation gave the required product **15** in 74% yield (Table 1, entry 9).[12b,13]

Next, the cyclotrimerization product **15** was subjected to acetylation followed by deprotection of the TBS group from the resulting diacetate **16** to prepare the penultimate benzyl alcohol **3** (Scheme 3). Finally, the sequential one-pot stepwise oxidation of benzyl alcohol **3**, first with Dess–Martin periodinane (DMP), followed by addition of *meta*-chloroperoxybenzoic acid (mCPBA), and then saponification of the crude Dakin oxidation[14] product by using 10% KOH in ethanol provided the targeted **2**. In the report on the isolation of **2**, the $^1H/^{13}C$ NMR spectra of the natural product were recorded in CD_3OD only.[2] However, synthetic **2** was neither completely soluble in CD_3OD nor in $CDCl_3$ alone except at very high dilution. Hence, the NMR spectrum was recorded in a mixture of CD_3OD and $CDCl_3$. The NMR spectroscopy data obtained for synthetic **2** deviated substantially from the data reported for the natural product. For ex-



Scheme 3. Completion of total synthesis of xylarinol B (**2**). TBAF = tetra-*n*-butylammonium fluoride.

ample, in the ^{13}C NMR spectrum, the triplet corresponding to C(1) of the oxepine unit was found to resonate at $\delta =$ 64.6 ppm, whereas the same carbon in the natural product resonated at $\delta = 71.6$ ppm. Additionally, the C(5) hydrogen in synthetic **2** was seen to resonate at $\delta = 3.5$ ppm downfield to that reported for the natural product. Additionally, a large difference in the specific rotation value between the natural and synthetic compound, with no reported melting point for the natural compounds, clearly indicates that the structure of **2** was wrongly assigned.

Next, the C(5)-diastereomer of **2** was synthesized starting with compound **9**β to evaluate the probable structure of **2**.[15] The spectral data obtained for C(5) epimer was different from synthetic **2** and also deviated substantially from naturally occurring **2**. At this stage, Professor B.-S Yun was contacted and he informed us that the structure of **2** was wrongly assigned and that its spectral data matched with previously isolated sordariol, with a dihydroisobenzofuran structure.[16] Interestingly, there are several reports on the isolation of sordariols from different sources; however, the relative structure of these compounds has been not proposed.

Conclusion

A cobalt-mediated bimolecular [2+2+2]-alkyne cyclotrimerization reaction has been successfully employed for the construction of the central benz-2-oxepine core of the proposed structure of **2**. This is the first example for constructing a seven-membered ring by employing intermolecular alkyne cyclotrimerization.

Experimental Section

General Methods

Reactions were carried out under a nitrogen/argon atmosphere in oven-dried glassware at RT unless otherwise stated. Standard inert atmosphere techniques were used in handling all air- and moisture-sensitive reagents. All anhydrous solvents were distilled prior to use: CH_2Cl_2 and DMF from CaH_2; MeOH on Mg cake; THF on Na/benzophenone, and $(Et)_3N$ over KOH. Petroleum ether refers to distilled light petroleum of fraction 30–40 °C. Bulk solutions were evaporated under reduced pressure by using a rotary evaporator. Brine refers to a saturated aqueous solution of NaCl. Na_2SO_4 was used for drying. Column chromatography was performed on 60–120, 100–200, 230–400 mesh size silica gel. Reactions were monitored by TLC, visualized under dual short/long wavelength UV light ($\lambda_{max} = 254$ and 365 nm.) and stained with *p*-anisaldehyde stains. ^1H NMR spectroscopy measurements were carried out on 200, 400, and 500 MHz NMR spectrometers, and $CDCl_3$ (δ 7.26) was used as an internal standard. ^{13}C NMR spectra were recorded on 200 (50 MHz), 400 (100 MHz), and 500 (125 MHz) NMR spectrometers. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane (TMS), and coupling constants (J) are given in Hz. Multiplicity is abbreviated as follows: s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of a doublet of doublets, t = triplet, dt = doublet of triplet, ddt = doublet of a doublet of triplets, q = quartet, dq = doublet of quartet, quin = quintet, qd = quartet of doublets, m = multiplet. The multiplicity of the ^{13}C NMR signals was assigned with the help of DEPT spectra and the abbreviations used were as follows: s = singlet, d = doublet, t = triplet, q = quartet, for C (quaternary), CH, CH_2, and CH_3 respectively. Specific optical rotations ($[a]_D^{25}$) were measured by using sodium light (D line $\lambda = 589$ nm) in $CHCl_3$ or CH_3OH. Mass spectra were recorded on a Hybrid Quadrupole-TOF LC/MS/MS spectrometer. HRMS was recorded on ESI-TOF mass spectrometers.

*3,6-Dideoxy-1,2-O-isopropylidene-5-O-pivaloyl-α-D-ribo-hexofuranose (**8**)*

At 0 °C, a solution of alcohol **7** (18 g, 95.6 mmol), Et_3N (26.7 mL, 191.3 mmol), and DMAP (0.23 g, 1.9 mmol) in anhydrous CH_2Cl_2 (100 mL) was treated with Piv-Cl (14.1 mL, 114.8 mmol) and stirred at the same temperature for 1 h and at RT for an additional 4 h. The reaction mixture was quenched at 0 °C with a saturated solution of $NaHCO_3$ (50 mL) and filtered through Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc (4×75 mL). The combined organic layer was washed with brine (2×100 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (5→15 % EtOAc in petroleum ether) gave ester **8** (23.6 g, 91 %) as a yellow syrup. $R_f = 0.7$ (EtOAc/petroleum ether, 1:4); $[a]_D^{25} = +1.15$ ($c = 0.6$, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max} = 2980$, 2932, 1731, 1480, 1373, 1282, 1216, 1161, 1060, 1025 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.16$ (s, 9H), 1.21 (d, $J = 6.4$ Hz, 3H), 1.3 (s, 3H), 1.50 (s, 3H), 1.72 (ddd, $J = 15.0$, 8.7, 4.7 Hz, 1H), 2.09 (dd, $J = 13.4$, 4.5 Hz, 1H), 4.15 (quin, $J = 5.2$ Hz, 1H), 4.71 (t, $J = 4.1$ Hz, 1H), 4.97 (t, $J = 6.3$ Hz, 1H), 5.77 ppm (d, $J = 3.4$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 16.8$ (q), 26.1 (q), 26.7 (q), 27.0 (q, 3C), 34.5 (t), 38.7 (s), 70.2 (d), 79.9 (d), 80.2 (d), 105.5 (d), 111.2 (s), 171.5 ppm (s); ESI-MS: *m/z* (%): 295.14 (100) $[M+Na]^+$; HRMS: *m/z* calcd for $C_{14}H_{24}NaO_5$: 295.152; found: 295.1519.

*Allyl 3,6-Dideoxy-5-O-pivaloyl-α/β-D-ribohexofuranose (**9**)*

p-TSA (1.9 g, 11.0 mmol) and allyl alcohol (7.5 mL, 110 mmol) were added to a solution of **8** (15.0 g, 55.1 mmol) in anhydrous THF (100 mL). The reaction mixture was heated at reflux for 4 h. After completion of the reaction, as indicated by TLC, the reaction mixture was neutralized with an aqueous solution of $NaHCO_3$ (20 mL). The solvent was removed under reduced pressure, diluted with EtOAc (200 mL), and washed with water (2×50 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel. First eluting with 10→20 % EtOAc in petroleum ether gave minor hexofuranoside **9**β (2.46 g, 17 %) as a thick yellow oil. $R_f = 0.3$ (EtOAc/petroleum ether, 1:4); $[a]_D^{25} = -75.0$ ($c = 0.77$, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max} = 3524$, 2977, 2935, 2873, 1730, 1646, 1480, 1457, 1397, 1282, 1237, 1160, 1080, 1035, 927, 869, 770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.16$ (s, 9H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.97 (m, 2H), 2.12 (brs, 1H), 3.92 (ddt, $J = 18.9$, 12.9, 6.2 Hz, 1H), 4.16 (ddt, $J =$ 17.9, 12.9, 5.1 Hz, 1H), 4.26 (m, 2H), 4.80 (quin, $J = 6.3$ Hz, 1H), 4.93 (s, 1H), 5.20 (dt, $J = 10.5$, 1.5 Hz, 1H), 5.28 (dt, $J = 17.1$, 1.3 Hz, 1H), 5.84 ppm (ddt, $J = 17.1$, 10.6, 5.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$):

δ=16.8 (q), 27.0 (q, 3C), 34.8 (t), 38.7 (s), 67.9 (t), 72.5 (d), 75.8 (d), 81.4 (d), 107.4 (d), 117.3 (t), 133.9 (s), 177.8 ppm (s); ESI-MS: *m/z* (%): 295.12 (30) $[M+Na]^+$; HRMS: *m/z* calcd for $C_{14}H_{24}NaO_5$: 295.1521; found: 295.1516.

Further eluting with 20→30% EtOAc in petroleum ether gave the major hexofuranoside **9**α (12.1 g, 80%) as a yellow viscous oil. R_f=0.2 (EtOAc/petroleum ether, 1:4); $[a]_D^{25}=+61.1$ (c=0.66, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=3460, 2979, 2935, 2875, 1730, 1481, 1457, 1397, 1283, 1162, 1086, 1034, 936, 865, 803, 770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.15 (d, J=6.7 Hz, 3H), 1.17 (s, 9H), 1.87 (ddd, J=15.7, 7.2, 5.4 Hz, 1H), 1.14 (ddd, J=12.9, 5.2, 4.9 Hz, 1H), 2.47 (d, J=9 Hz, 1H), 4.06 (ddt, J=12.9, 6.1, 1.3 Hz, 1H), 4.17 (dd, J=4.5 Hz, 1H), 4.3 (m, 2H), 4.92 (ddd, J=12.9, 6.5, 4.2 Hz, 1H), 4.97 (d, J=4.3 Hz, 1H), 5.18 (dq, J=10.4, 1.5 Hz, 1H), 5.27 (dq, J=17.2, 1.5 Hz, 1H), 5.92 ppm (ddt, J=17.1, 10.6, 5.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=16.2 (q), 27.1 (q, 3C), 32.9 (t), 38.7 (s), 68.6 (t), 70.9 (d), 71.8 (d), 78.8 (d), 100.8 (d), 117.3 (t), 134.0 (s), 177.7 ppm (s); ESI-MS: *m/z* (%): 295.14 (100) $[M+Na]^+$; HRMS: *m/z* calcd for $C_{14}H_{24}NaO_5$: 295.1521; found: 295.1520. The diastereomeric ratio was evaluated by the yields of the pure diastereomers (α/β, 4:1).

*Allyl 3,6-Dideoxy-2-O-(p-nitrobenzoyl)-5-O-pivaloyl-α-D-arabinohexofuranoside (**10**)*

A solution of alcohol **9**α (2.5 g, 9.2 mmol), *p*-nitrobenzoic acid (8.41 g, 45.9 mmol), and PPh_3 (8.43 g, 32.1 mmol) in THF (50 mL) was treated with diisopropylazodicarboxylate (6.33 mL, 32.1 mmol) and the contents were stirred at 0 °C for 1 h and then at RT for 5 h. After completion, the reaction mixture was concentrated and the resulting crude product was dissolved in EtOAc (200 mL), washed with an aqueous solution of $NaHCO_3$ (30 mL) and water (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (8→10% EtOAc in petroleum ether) gave ester **10** (2.78 g, 72%) as a yellow oil. R_f=0.6 (EtOAc/petroleum ether, 1:2); $[a]_D^{25}=+21.7$ (c=0.16, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=2972, 2318, 1728, 1607, 1530, 1271, 1104, 1042, 869, 770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.16 (s, 9H), 1.27 (d, J=6.3 Hz, 3H), 1.88 (ddd, J=7.8, 5.8, 2.0 Hz, 1H), 2.57 (ddd, J=14.6, 7.9, 6.9 Hz, 1H), 4.02 (ddt, J=18.9, 12.9, 5.9 Hz, 1H), 4.18 (m, 2H), 5.02 (quin, J=6.3 Hz, 1H), 5.2 (dq, J=2.8, 1.5, 1.2 Hz, 1H), 5.22 (s, 1H), 5.3 (dq, J=3.2, 1.6 Hz, 1H), 5.35 (m, 1H), 5.89 (ddt, J=17.1, 10.6, 5.4 Hz, 1H), 8.2 (dt, J=9.1, 3.9 Hz, 2H), 8.30 ppm (dt, J=9.1, 3.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=16.7 (q), 27.0 (q, 3C), 32.2 (t), 38.7 (s), 67.9 (q), 70.8 (d), 79.1 (d) 79.9 (d), 105.1 (d), 117.5 (d), 123.6 (d, 2C), 130.8 (d, 2C), 133.8 (s), 134.9 (s), 150.7 (s), 164.0 (s), 177.6 ppm (s); ESI-MS: *m/z* (%): 444.16 (50) $[M+Na]^+$; HRMS: *m/z* calcd for $C_{21}H_{27}NNaO_8$: 444.1634; found: 444.1632.

*Allyl 3,6-Dideoxy-α-D-arabinohexofuranoside (**11**)*

At 0 °C, a solution of **10** (2.0 g, 4.7 mmol) in dry THF (10 mL) was treated with $LiAlH_4$ (0.45 g, 11.9 mmol) and the contents were stirred for 4 h at RT. The reaction mixture was quenched with a saturated solution of Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in EtOAc (100 mL) and filtered through Celite. The organic layer was washed with water (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (40→50% EtOAc in petroleum ether) afforded diol **11** (0.86 g, 96%) as a yellow syrup. R_f=0.2 (EtOAc/petroleum ether, 1:1); $[a]_D^{25}=+91.7$ (c=0.38, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=3369, 2972, 2925, 1599, 1457, 1096, 1044, 1018, 933 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.14 (d, J=6.7 Hz, 3H), 1.8 (dd, J=13.9, 2.9 Hz, 1H), 2.29 (dq, J=14.0, 5.6 Hz, 1H), 2.57 (brs, 1H), 3.69 (brs, 1H), 3.96 (ddt, J=18.9, 13.0, 6.1 Hz, 1H), 4.0–4.2 (m, 4H), 4.97 (s, 1H), 5.17 (dq, J=10.2, 1.8 Hz, 1H), 5.26 (dq, J=17.2, 1.6 Hz, 1H), 5.86 ppm (ddt, J=16.2, 11.2, 5.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=19.3 (q), 30.6 (t), 67.4 (d), 67.8 (t), 73.8 (d), 81.8 (d), 107.4 (d), 117.1 (t), 134.3 ppm (d); ESI-MS: *m/z* (%): 211.08 (10) $[M+Na]^+$; HRMS: *m/z* calcd for $C_9H_{16}NaO_4$: 211.0946; found: 211.0943.

*Allyl 3,6-Dideoxy-2,5-di-O-(p-methoxybenzyl)-α-D-arabinohexofuranoside (**12**)*

NaH (1.44 g, 60.1 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of **11** (2.83 g, 15.0 mmol) in anhydrous DMF/THF (1:1, 30 mL) cooled on an ice bath and stirred for 5 min. Then *p*-anisyl chloride (1.2 mL, 60.1 mmol) was added dropwise and stirring was continued at RT for 3 h. After completion of the reaction, the reaction mixture was cooled and quenched with an aqueous solution of NH_4Cl. The solvent was removed under reduced pressure, the crude product was diluted with EtOAc, and washed with water (3×50 mL). The aqueous layer was extracted with EtOAc (2×100 mL) and the combined organic layer was washed with brine (2×50 mL) and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (5→10% EtOAc in pet. ether) gave **12** (6.1 g, 95%) as a yellow oil. R_f=0.3 (EtOAc/petroleum ether, 1:9); $[a]_D^{25}=+18.4$ (c=0.23, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=2912, 1611, 1513, 1464, 1369, 1297, 1247, 1174, 1096, 1034, 821, 792 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.21 (d, J=6.2 Hz, 3H), 1.92 (ddd, J=9.7, 6.6, 3.2 Hz, 1H), 2.28 (quin, J=7.5 Hz, 1H), 3.59 (quin, J=6.2 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 3.92 (ddt, J=17.4, 12.9, 5.9 Hz, 1H), 3.98–4.06 (m, 2H), 4.16 (ddt, J=18.1, 12.9, 5.2 Hz, 1H), 4.40 (s, 2H), 4.52 (dd, J=15.8, 11.4 Hz, 2H), 5.09 (s, 1H), 5.15 (dq, J=10.2, 1.6 Hz, 1H), 5.26 (dq, J=11.3, 1.8 Hz, 1H), 5.9 (ddt, J=17.1, 10.6, 5.4 Hz, 1H), 6.81 (d, J=8.7 Hz, 2H), 6.85 (d, J=8.7 Hz, 2H), 7.20 (d, J=8.7 Hz, 2H), 7.24 ppm (d, J=8.8 Hz 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=16.7 (q), 32.4 (t), 55.2 (q, 2C), 67.8 (t), 70.8 (t), 70.9 (t), 76.2 (d), 81.5 (d), 82.9 (d), 105.9 (d), 113.7 (d, 2C), 113.7 (t, 2C), 117.0 (t), 129.2 (d, 2C), 129.3 (d, 2C), 130.1 (d), 130.9 (s), 134.4 (s), 159.0 (s), 159.1 ppm (s); ESI-MS: *m/z* (%): 451.19 (100) $[M+Na]^+$; HRMS: *m/z* calcd for $C_{25}H_{32}NaO_6$: 451.2096; found: 451.2092.

*(2R,3S,5S)-2,5-Bis(4-methoxybenzyl)hept-6-yn-2,3,5-triol (**5**)*

A solution of **12** (0.2 g, 0.47 mmol) in EtOH was added to a suspension of NNDMBA (90 mg, 0.56 mmol), $[Pd(PPh_3)_4]$ (6 mg, 5 mol%), and PPh_3 (25 mg, 0.93 mmol) in absolute EtOH (15 mL) and stirred for 6 h at RT. After completion of the reaction, as indicated by TLC, the content was filtered through Celite and the filtrate was concentrated. The residue was passed through a short column of silica gel (10→30% EtOAc in pet. ether) to give the crude lactal (180 mg) as a yellow liquid, which was used in the next reaction without further purification.

A solution of **13** (180 mg, 0.93 mmol) in THF (1 mL) was added in three portions to a suspension of the above crude lactal (180 mg) and oven-dried K_2CO_3 (0.32 g, 2.3 mmol) in THF and MeOH (1:1, 10 mL) over 45 min at RT. After 15 h, the solvent was removed under reduced pressure, diluted with CH_2Cl_2 (25 mL), and filtered through Celite. The organic layer was washed with water (3×5 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (20→30% EtOAc in petroleum ether) gave alkynol **5** (145 mg, 81%, over 2 steps) as a yellow oil. R_f=0.7 (EtOAc/petroleum ether, 3:7); $[a]_D^{25}=-75.7$ (c=0.82, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=3280, 2923, 2840, 1611, 1513, 1456, 1382, 1294, 1247, 1173, 1073, 1033, 820, 773 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.15 (d, J=6.3 Hz, 3H), 1.89 (m, 2H), 2.48 (d, J=2.0 Hz, 1H), 2.52 (d, J=4.0 Hz, 1H), 3.45 (qd, J=5.9, 1.8 Hz, 1H), 3.79 (s, 6H), 3.98 (td, J=7.6, 3.7 Hz, 1H), 4.33 (m, 1H), 4.37 (d, J=11.5 Hz, 1H), 4.42 (d, J=11.4 Hz, 1H), 4.63 (d, J=11.4 Hz, 1H), 4.74 (d, J=11.1 Hz, 1H), 6.85 (d, J=8.4 Hz, 2H), 6.85 (d, J=8.7 Hz, 2H), 7.22 (d, J=7.4 Hz, 2H), 7.24 ppm (d, J=8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.4 (q), 37.9 (t), 55.2 (q, 2C), 65.7 (d), 70.2 (d), 70.4 (t), 70.5 (t), 74.1 (d), 77.0 (d), 82.6 (s), 113.8 (d, 4C), 129.2 (d, 2C), 129.5 (s), 129.7 (d, 2C), 130.6 (s), 159.1 (s), 159.3 ppm (s); ESI-MS: *m/z* (%): 407.11 (100) $[M+Na]^+$; HRMS: *m/z* calcd for $C_{23}H_{28}NaO_5$: 407.1834; found: 407.1834.

*(3S,5S)-3-Ethynyl-5-{(R)-1-[(4-methoxybenzyl)oxy]ethyl}-1-(4-methoxyphenyl)-12,12,13,13-tetramethyl-2,6,11-trioxa-12-silatetradec-8-yne (**14**)*

NaH (60% dispersion in mineral oil, 63 mg, 1.6 mmol) was added portionwise to a solution of alkynol **5** (0.3 g, 0.78 mmol) in anhydrous THF/DMF (1:1, 6 mL) cooled on an ice bath. After 15 min, compound **6**

(364 mg, 1.2 mmol) was introduced and the contents were stirred for 6 h at RT. After completion of the reaction, the reaction mixture was quenched with an aqueous solution of NH_4Cl, concentrated under reduced pressure, and diluted with EtOAc (50 mL). The organic layer was washed with water (2×30 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10→20% EtOAc in petroleum ether) to give diyne **14** (370 mg, 84%) as a yellow oil. R_f=0.5 (EtOAc/petroleum ether, 1:6); $[a]_D^{25}$=−54.9 (c=0.32, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=2929, 2851, 2648, 2049, 1611, 1513, 1457, 1363, 1248, 1176, 1077, 1034, 836, 775 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.08 (s, 6H), 0.88 (s, 9H), 1.12 (d, J=6.4 Hz, 3H), 1.9 (m, 2H), 2.43 (d, J=1.9 Hz, 1H), 3.60 (qd, J=3.7, 2.8 Hz, 1H), 3.71 (m, 1H), 3.79 (s, 6H), 4.09 (dt, J=15.7, 3.8 Hz, 1H), 4.23–4.35 (m, 4H), 4.43 (d, J=11.1 Hz, 1H), 4.48 (s, 2H), 4.73 (d, J=11.0 Hz, 1H), 6.83 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 7.23 (d, J=7.4 Hz, 2H), 7.26 ppm (d, J=8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−5.2 (q, 2C), 15.1 (q), 18.3 (s), 25.8 (q, 3C), 37.7 (t), 51.7 (t), 55.3 (d, 2C), 58.3 (t), 64.9 (d), 70.4 (t), 70.7 (t), 73.5 (d), 76.2 (d), 77.4 (d), 81.4 (s), 83.2 (s, 2C), 113.7 (d, 2C), 113.8 (d, 2C), 129.1 (d, 2C), 129.7 (s), 129.9 (d, 2C), 130.5 (s), 159.3 ppm (s, 2C); ESI-MS: m/z (%): 589.28 (100) $[M+Na]^+$; HRMS: m/z calcd for $C_{33}H_{46}NaO_6Si$: 589.2961; found: 589.2960.

*(2R,3S,5S)-3-({4-[(tert-Butyldimethylsilyl)oxy]but-2-yn-1-yl}oxy)hept-6-yne-2,5-diol (**4**)*

At 0°C, DDQ (0.7 g, 3.1 mmol) was added to a vigorously stirred solution of diyne **14** (0.35 g, 0.62 mmol) in CH_2Cl_2/phosphate buffer solution (20:1, 5 mL, pH 7.2) and the contents were allowed to come to RT and stirred for 12 h. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL), diluted with CH_2Cl_2, and filtered through Celite. The organic layer was washed with water (60 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the resulting crude by column chromatography (30→60% EtOAc in petroleum ether) gave diol **4** (185 mg, 92%) as a thick colorless oil. R_f=0.3 (EtOAc/petroleum ether, 3:2); $[a]_D^{25}$=−27.4 (c=0.24, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=3296, 2926, 2855, 1717, 1603, 1457, 1257, 1127, 1084, 1023, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.12 (s, 6H), 0.91 (s, 9H), 1.15 (d, J=6.4 Hz, 3H), 1.81 (ddd, J=11.3, 8.8, 2.5 Hz, 1H), 1.93 (ddd, J=13.2, 10.2, 2.8 Hz, 1H), 2.03 (br s, 1H), 2.43 (d, J=2.0 Hz, 1H), 3.28 (br s, 1H), 3.81 (dt, J=10.3, 5.3 Hz, 1H), 4.06 (qd, J=3.5, 3.0 Hz, 1H), 4.30 (d, J=1.1 Hz, 2H), 4.33 (s, 2H), 4.65 ppm (d, J=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−5.3 (q, 2C), 17.6 (q), 18.4 (s), 25.8 (q, 3C), 35.9 (t), 51.8 (t), 57.7 (t), 58.8 (d), 67.5 (d), 72.4 (d), 79.3 (d), 81.2 (s), 84.8 (s), 85.1 ppm (s); ESI-MS: m/z (%): 349.15 (100) $[M+Na]^+$; HRMS: m/z calcd for $C_{17}H_{30}NaO_4Si$: 349.181; found: 349.1809.

*(3S,5S)-9-{[(tert-Butyldimethylsilyl)oxy]methyl}-3-[(R)-1-hydroxyethyl]-1,3,4,5-tetrahydrobenzo[c]oxepin-5-ol (**15**)*

A sealed tube containing a solution of diol **4** (78 mg, 0.24 mmol) in toluene (2 mL) and $[Cp(CO)_2Co]$ (0.7 mL, 0.35 M in toluene, 0.24 mmol) was fitted with a septum and cooled to −78°C. Acetylene gas was bubbled through the reaction mixture for 20 min. The tube was then sealed with a screw cap and stirred while irradiated with a 200 W bulb kept 2 cm away from the tube. After 15 h, the reaction mixture was cooled and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (40→50% EtOAc in petroleum ether) to afford **15** (62 mg, 74%) as a thick colorless oil. R_f=0.3 (EtOAc/petroleum ether, 1:1); $[a]_D^{25}$=−29.8 (c=0.26, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=3406, 3016, 2912, 2846, 1602, 1489, 1456, 1218, 1113, 1031, 757, 724, 694, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=0.04 (s, 3H), 0.07 (s, 3H), 0.9 (s, 9H), 1.15 (d, J=6.4 Hz, 3H), 2.08 (m, 3H), 3.81 (dt, J=9.8, 4.1 Hz, 1H), 3.87 (qd, J=3.0, 2.9 Hz, 1H), 4.56 (d, J=15 Hz, 1H), 4.66 (d, J=12.8 Hz, 1H), 4.77 (d, J=12.8 Hz, 1H), 5.03 (dd, J=6.7, 2.7 Hz, 1H), 5.23 (d, J=14.9 Hz, 1H), 7.27 (d, J=5.8 Hz, 1H), 7.28 (t, J=5.5 Hz, 1H), 7.42 ppm (dd, J=5.5 Hz, 1H);^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.3 (q), −5.2 (q), 17.9 (q), 18.3 (s), 25.9 (q, 3C), 37.9 (t), 63.5 (t), 68.3 (t), 69.9 (d), 72.4 (d), 83.8 (d), 125.2 (d), 127.0 (d), 127.6 (d), 134.3 (s), 138.3 (s), 143.5 ppm (s); ESI-MS: m/z (%): 375.10 (100) $[M+Na]^+$; HRMS: m/z calcd for $C_{19}H_{32}NaO_4Si$: 375.1967; found: 379.1965.

*(R)-1-(3S,5S)-5-Acetoxy-9-{[(tert-butyldimethylsilyl)oxy]methyl}-1,3,4,5-tetrahydrobenzo[c]oxepin-3-yl}ethyl acetate (**16**)*

Ac_2O (0.1 mL) was added to a solution of diol **15** (45 mg, 0.13 mmol), Et_3N (0.2 mL, 1.3 mmol), and DMAP (2 mg) in CH_2Cl_2 (5 mL) at RT. After 2 h, water was added to the reaction mixture, which was extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was washed with brine (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (10→30% EtOAc in petroleum ether) gave **16** (54 mg, 97%) as a colorless thick oil. R_f=0.5 (EtOAc/petroleum ether, 1:4); $[a]_D^{25}$=−24.9 (c=0.52, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=3439, 2923, 2840, 1739, 1613, 1492, 1456, 1360, 1237, 1116, 1031, 861, 757, 724, 691, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=0.02 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.20 (d, J=6.4 Hz, 3H), 1.85 (dt, J=13.1, 11 Hz, 1H), 2.01–2.08 (m, 1H), 2.05 (s, 3H), 2.22 (s, 3H), 3.95 (ddd, J=6.4, 4.6, 1.8 Hz, 1H), 4.41 (d, J=14.4 Hz, 1H), 4.71 (d, J=12.8 Hz, 1H), 4.84 (d, J=12.2 Hz, 1H), 4.85 (ddd, J=12.9, 6.5, 4.5 Hz, 1H), 5.20 (d, J=14.4 Hz, 1H), 6.21 (dd, J=10.4, 1.5 Hz, 1H), 7.24–7.30 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.3 (q), −5.2 (q), 15.6 (q), 18.2 (s), 21.2 (q), 21.3 (q), 25.9 (q, 3C), 37.2 (t), 63.4 (t), 66.4 (t), 72.4 (d), 72.5 (d), 82.5 (d), 123.0 (d), 127.0 (d), 127.8 (d), 134.1 (s), 138.9 (s) 141(s), 169.8 (s), 170.4 ppm (s); HRMS: m/z calcd for $C_{23}H_{36}NaO_6Si$: 459.2178; found: 459.2181.

*(R)-1-((3S,5S)-5-Acetoxy-9-(hydroxymethyl)-1,3,4,5-tetrahydrobenzo[c]oxepin-3-yl)ethyl acetate (**3**)*

TBAF (44 mg, 0.17 mmol, 1 M in THF) was added to a solution of **16** (48 mg, 0.11 mmol) in anhydrous THF (3 mL) cooled on an ice bath. The reaction mixture was then stirred at RT for 30 min and concentrated. The crude product was dissolved in EtOAc (30 mL), washed with water (2×10 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (50→70% EtOAc in petroleum ether) gave **3** (32 mg, 90%) as a yellow oil. R_f=0.3 (EtOAc/petroleum ether, 1:1); $[a]_D^{25}$=−29.5 (c=0.36, $CHCl_3$); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=3434, 2917, 2846, 1739, 1607, 1454, 1374, 1240, 1116, 1039, 751, 655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.22 (d, J=6.4 Hz, 3H), 1.85 (dt, J=13.4, 10.7 Hz, 1H), 2.03 (s, 1H), 2.05 (s, 3H), 2.23 (s, 3H), 3.98 (ddd, J=6.9, 2.3 Hz, 1H), 4.47 (d, J=14.4 Hz, 1H), 4.76 (d, J=6.9 Hz, 2H), 4.83 (qd, J=6.6, 4.7 Hz, 1H), 5.28 (d, J=14.6 Hz, 1H), 6.22 (dd, J=10.6, 2.1 Hz, 1H), 7.26 (d, J=7.6 Hz, 1H), 7.28 (d, J=7.5 Hz, 1H), 7.32 ppm (t, J=7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=15.6 (q), 21.2 (q), 21.3 (q), 37.2 (t), 63.5 (t), 66.6 (t), 72.3 (d), 72.4 (d), 82.8 (d), 123.8 (d), 128.1 (d, 2C), 134.8 (s), 138.4 (s), 141.5 (s), 169.7 (s), 170.4 ppm (s); ESI-MS: m/z (%): 345.09 (30) $[M+Na]^+$; HRMS: m/z calcd for $C_{17}H_{22}NaO_6$: 345.1313; found: 345.1312.

*Synthetic Xylarinol B (**2**)*

DMP (52 mg, 0.12 mmol) was added to a solution of alcohol **3** (26 mg, 0.08 mmol) in dry CH_2Cl_2 (5 mL) cooled on an ice bath. After complete consumption of **3**, as indicated by TLC, mCPBA (40 mg, 70%, 0.16 mmol) was added and the solution was stirred at RT for another 6 h. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The resulting crude product, after evaporation of CH_2Cl_2, was taken up in ethanol (5 mL), cooled to 0°C, and treated with 10% KOH in water (5 mL). After 10 h, the reaction was neutralized with 10% HCl (36%, 5 mL) and the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc (50 mL), filtered through Celite, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (60→80% EtOAc in petroleum ether) afforded **2** (12 mg, 67% over 3 steps) as a yellow solid. R_f=0.3 (EtOAc/petroleum ether, 4:1); m.p. 62–63°C; $[a]_D^{25}$=−47.8 (c=0.43, MeOH); FTIR (KBr, $CHCl_3$): $\tilde{\nu}_{max}$=3401, 2912, 1640, 1492, 1465, 1273, 1215, 1124, 1034, 856, 762, 727, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$+CD_3OD): δ=1.16 (d, J=6.4 Hz, 3H), 1.71 (dt, J=13.5, 10.4 Hz, 1H), 2.16 (dt, J=13.4, 2.2 Hz, 1H), 3.68 (m, 2H), 4.26 (d, J=13.7 Hz, 1H), 5.00 (d, J=9.5 Hz, 1H), 5.41 (d, J=14.0 Hz, 1H), 6.69 (d, J=7.9 Hz,

1H), 7.05 (d, $J=7.3$ Hz, 1H), 7.08 ppm (t, $J=7.9$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$): $\delta=18.6$ (q), 40.3 (t), 64.6 (t), 70.4 (d), 71.3 (d), 86.1 (d), 114.4 (d), 115.7 (d), 122.8 (s), 128.8 (d), 147.2 (s), 154.6 ppm (s); ESI-MS: *m/z* (%): 247.01 (25) $[M+Na]^+$; HRMS: *m/z* calcd for $C_{12}H_{16}NaO_4$: 247.0946; found: 247.0944.

Acknowledgements

We would like to acknowledge the CSIR (India) for providing the financial support for this project under the 12FYP ORIGIN program. A.A.M. thanks UGC (New Delhi) for financial assistance in the form of a Research Fellowship.

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Received: December 11, 2013
Revised: January 31, 2014
Published online: March 27, 2014