First total synthesis of kipukasin A

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Full Research Paper

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Abstract
In this paper, a practical approach for the total synthesis of kipukasin A is presented with 22% overall yield by using tetra-O-acetyl-β-D-ribose as starting material. An improved iodine-promoted acetonide-forming reaction was developed to access 1,2-O-isopropylidene-α-D-ribofuranose. For the first time, ortho-alkynylbenzoate was used as protecting group for the 5-hydroxy group. After subsequent Vorbrüggen glycosylation, the protecting group could be removed smoothly in the presence of 5 mol % Ph₃PAuOTf in dichloromethane to provide kipukasin A in high yield and regioselectivity.

Introduction
Endogenous nucleosides are involved in DNA and RNA synthesis, cell signalling, enzyme regulation and metabolism etc. [1,2]. Therefore, the synthesis of novel nucleosides to mimic their physiological counterparts has potential therapeutic significance, which has led to the development of a large number of antiviral and antitumor drugs [3,4]. On the other hand, naturally occurring nucleosides, especially marine nucleosides, have also played an indispensable role in drug discovery, which make great contribution in the commercialization of cytosine arabinoside (Ara-C), adenine arabinoside (Ara-A) and AZT, etc. [5,6]. Nucleosides and their analogues will continue to play an important role in future drug discovery [7].

In the past decades, exploration of novel naturally occurring marine nucleosides has made expeditious achievements [8-10]. Some of them showed promising antibiotic, antiviral, antiparasitic and antitumor properties. Kipukasins A–G were firstly isolated from solid-substrate fermentation cultures of Hawaiian Aspergillus Versicolor in 2007 (Figure 1) [11]. Later on, kipukasins H, I [12] and J [13] were also isolated from the fungus Aspergillus flavus, which was collected at the South China Sea and the Sea of Okhotsk, respectively. Kipukasins are uridine derivatives with unique structural characteristics, which include: (1) a uracil moiety with or without an N-3 methyl group; (2) a 6-methyl-2,4-hydroxy (or methoxy)-benzoyl group at C-2’ or C-3’ position; (3) with or without an acetyl group at 2’-OH position. To the best of our knowledge, they are the first naturally occurring aroyl nucleosides reported up to now. The biological assays showed that kipukasin A...
owned modest activity against Gram-positive bacteria *Staphylococcus aureus* (ATCC 29213) [11].

During our ongoing biological studies of marine nucleosides, total syntheses of several marine nucleosides were accomplished in our group [14-18]. In the present paper, we reported a practical approach for the total synthesis of kipukasin A.

**Results and Discussion**

From the synthetic point of view, it seemed that the most direct approach for the synthesis of kipukasin A was the regioselective modification of commercially available uridine (Figure 2, path a). After carefully assessment, we realized that it would require several steps of protection and deprotection. Especially under alkaline conditions, 2',3'-transesterification is inevitable

![Figure 1: Structures of kipukasins A–J.](image)

kipukasin A; R¹ = R² = CH₃, R³ = H
kipukasin B; R¹ = CH₃, R² = R³ = H
kipukasin C; R¹ = R² = H, R³ = CH₃
kipukasin F; R¹ = R³ = CH₃, R² = H
kipukasin J; R¹ = R² = H, R³ = CH₃
kipukasin D; R¹ = CH₃, R² = H
kipukasin G; R¹ = H, R² = CH₃
kipukasin I; R¹ = R² = H
kipukasin E; R = CH₃
kipukasin H; R = H

![Figure 2: Retrosynthetic analysis of kipukasin A.](image)
to occur in nucleosides [19-21]. The synthetic route would be lengthy and cumbersome. Therefore, a practical total synthesis is in high demand to facilitate the preparation of other kipukasins and their analogues.

The retrosynthetic analysis is shown in Figure 2 (path b). Kipukasin A could be constructed by Vorbrüggen glycosylation [22,23] of a properly protected glycosyl donor 3 with uracil (4). Neighboring group participation of the 2'-O-acetyl group stereoselectively facilitate the β-glycosidic bond formation. Thus, the choice of a suitable protecting group at 5-OH position would be crucial for the success. It should fulfill at least two requirements: (1) it should be stable during the Vorbrüggen glycosylation; and (2) the deprotection process should be performed under very mild and neutral conditions without any influence on the 2'-O-acetyl group. At the same time, ester protection is preferred for Vorbrüggen glycosylations in nucleoside syntheses. Very recently, ortho-alkynylbenzoate was successfully developed by our group as neighboring participation group to synthesize 2'-modified nucleosides [24], which could be removed smoothly in the presence of gold(I) complexes with high yield and selectivity. The conditions are very mild and neutral. In the present paper, we continue to use ortho-alkynylbenzoate as protecting group for the 5'-OH group to synthesize 5'-diacetyl-2'-modified nucleosides [24]. The structure of 5'-diacetyl-1,2- isopropylidene-D-ribofuranose (11) was unambiguously confirmed by X-ray diffraction analysis (Figure 3) [34]. Then Sonogashira cross-coupling with 1-hexyne provided 1,2-O-isopropylidene-D-ribofuranose (12) in 93% yield. Subsequently, the reaction of 1,2-O-isopropylidene-D-ribofuranose (12) with 2-iodobenzoyl chloride (0.9 equiv) gave the corresponding 5'-O-benzoyl ester 13 in 80% yield along with a small amount of the 3,5-dibenzyol ester. The structure of 5'-O-benzoyl ester 13 was unambiguously confirmed by X-ray diffraction analysis (Figure 3) [34]. Then Sonogashira cross-coupling with 1-hexyne provided ribose 14 in 78% yield [35].

According to the retrosynthetic analysis, we firstly started to synthesize of aryl building block 9 (Scheme 1). Vilsmeier formylation of 1,3-dihydroxy-5-methylbenzene (5) gave 2,4-di-hydroxy-6-methylbenzaldehyde (6) in 75% yield [25,26]. Then compound 6 could react with methyl iodine in acetone by using K2CO3 as base. The obtained 2,4-dimethoxy-6-methylbenzaldehyde (7) was further oxidized with NaH2PO4/NaClO2 in DMSO to provide 2,4-dimethoxy-6-methylbenzoic acid (8) in 81% yield [27,28]. Finally, 2,4-dimethoxy-6-methylbenzoyl chloride (9) was obtained by refluxing with oxalyl chloride in dichloromethane. After removing the solvent and excess oxalyl chloride, 2,4-dimethoxy-6-methylbenzoyl chloride (9) was used directly in the next step without further purification.

Then we started to synthesize glycosylation donor 16 as the key building block (Scheme 2). In previous reports, 3,5-O-diacyetyl-1,2-O-isopropylidene-D-ribofuranose (11) was prepared either from D-xylose [29-31] or from tetra-O-acetyl-β-D-ribose (10) [32,33]. In 2009, Koreeda reported an iodine-promoted acetonide-forming reaction of tetra-O-acetyl-β-D-ribose (10) [33]. In this preliminary paper, 25 mol % of iodine was necessary. After systematic optimization, it was found that 6 mol % iodine could complete the reaction efficiently in freshly dried acetone to give 3,5-O-diacyetyl-1,2-O-isopropylidene-D-ribofuranose (11) in 88% yield. Then cleavage of the remaining acetyl groups by K2CO3 in MeOH afforded 1,2-O-isopropylidene-D-ribofuranose (12) in 93% yield. Subsequently, the reaction of 1,2-O-isopropylidene-D-ribofuranose (12) with 2-iodobenzoyl chloride (0.9 equiv) gave the corresponding 5-O-benzoyl ester 13 in 80% yield along with a small amount of the 3,5-dibenzoyl ester. The structure of 5'-O-benzoyl ester 13 was unambiguously confirmed by X-ray diffraction analysis (Figure 3) [34]. Then Sonogashira cross-coupling with 1-hexyne provided ribose 14 in 78% yield [35].

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Scheme 1: Synthesis of 2,4-dimethoxy-6-methylbenzoic chloride. Reagents and conditions: (a) POCl3, DMF, 0 °C to rt, 75%; (b) MeI, K2CO3, acetone, rt, 93%; (c) NaClO2, NaH2PO4, DMSO, rt, 81%; (d) (COCl)2, CH2Cl2, reflux.
Scheme 2: Total synthesis of kipukasin A. Reagents and conditions: (a) I$_2$, acetone, 0 °C to rt, 88%; (b) K$_2$CO$_3$, MeOH, rt, 93%; (c) 2-iodobenzoyl chloride, pyridine, -10 °C to rt, CH$_2$Cl$_2$, 80%; (d) 1-hexyne, PdCl$_2$(PPh$_3$)$_3$, CuI, Et$_3$N, THF, 50 °C, 78%; (e) 9, DMAP, Et$_3$N, CH$_2$Cl$_2$, 0 °C to rt, 74%; (f) Ac$_2$O, H$_2$SO$_4$, acetic acid, rt, 74%; (g) uracil, BSA, TMSOTf, MeCN, 75 °C, 89%; (h) 5% Ph$_3$PAuOTf, H$_2$O, CH$_2$Cl$_2$, EtOH, rt, 90%.

With glycosylation donor 16 in hand, we proceeded to investigate the crucial Vorbrüggen glycosylation with uracil (4). To our delight, in a similar manner as our described in [17], it proved to be efficient to give nucleoside 17 with exclusive β-configuration in 89% yield. At last, using our developed approach [24], kipukasin A was obtained in 90% yield in the presence of 5 mol % Ph$_3$PAuOTf in dichloromethane with H$_2$O (1 equiv) and ethanol (6 equiv). All spectra of the synthetic kipukasin A were consistent with an authentic sample.

**Conclusion**

In summary, the first total synthesis of kipukasin A was accomplished with 22% overall yield. The reaction sequence includes: (1) an improved iodine-promoted acetonide-forming reaction to...
synthesize 1,2-O-isopropylidene-D-ribofuranose (12); (2) a Vöhringen glycosylation facilitating the preparation for kipukasin derivatives and (3) the first use of ortho-alkynylbenzoate as protecting group of the 5-hydroxy group, which can be removed smoothly in the presence of 5 mol % Pd3PauOTf in dichloromethane. Biological studies of kipukasin A and the total synthesis of other kipukasin nucleosides by this established approach are ongoing in our group.

**Experimental**

All reagents and catalysts were purchased from commercial sources (Acros or Aldrich) and used without purification. DCM and CH3CN were dried over CaH2 and distilled prior to use. Et3N was dried over NaH and distilled prior to use. Thin-layer chromatography was performed using silica gel GF-254 plates with detection by UV (254 nm) or charting with 10% sulfuric acid in ethanol. Column chromatography was performed on silica gel (200–300 mesh, Qing-Dao Chemical Company, China). NMR spectra were recorded on a Bruker AV400 spectrometer, and chemical shifts (δ) are reported in ppm. 1H NMR and 13C NMR spectra were calibrated with TMS as internal standard, and coupling constants (J) are reported in Hz. The ESI-HRMS were obtained on an AB SCIEX Triple TOF 4600 spectrometer in positive ion mode. Melting points were measured on an electrothermal apparatus and are uncorrected. Optical rotation values were measured with a Rudolphautopol polarimeter.

**Synthesis of 3,5-O-diacyetyl-1,2-O-isopropylidene-D-ribofuranose (11):** To a solution of 1,2,3,5-O-acyethyl-β-D-ribofuranose (10, 10.0 g, 31.4 mmol) in dry acetone (100 mL) was added I2 (0.5 g, 2.0 mmol) at 0 °C under argon. After addition, the solution was stirred for 5 h at room temperature and quenched with 40 mL Na2S2O3 (3.0 g, 19.0 mmol). The solvent was evaporated under reduced pressure and distilled water (200 mL) was added to the residue. After that, the solution was extracted with CH2Cl2 (100 mL × 3), the combined organic layer was washed with sat. aq NaHCO3 (100 mL), brine (100 mL), and dried with anhydrous Na2SO4. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, PE/EtOAc 1:2; v:v) to afford 11 as a light-yellow oil (7.6 g, 88%). [α]D25 +133.3 (c 0.1, acetone) (lit. [37] [α]D25 +125.9 (c 1.1, CHCl3); 1H NMR (400 MHz, DMSO-d6) δ 5.81 (d, J = 3.7 Hz, 1H), 4.77 (t, J = 4.2 Hz, 1H), 4.67 (dd, J = 9.1, 4.8 Hz, 1H), 4.24 (dd, J = 12.1, 2.7 Hz, 1H), 4.20–4.15 (m, 1H), 4.05 (dd, J = 12.1, 5.4 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.45 (s, 3H), 1.27 (s, 3H); 13C NMR (101 MHz, DMSO-d6) δ 170.1, 169.7, 112.2, 103.9, 76.8, 75.1, 71.9, 62.4, 26.4, 20.5, 20.4; LRMS (ESI) m/z: 297.2 [M + Na]+; HRMS (ESI) m/z: [M + Na]+ cale for C12H18O7Na, 297.0945; found, 297.0943.

**Synthesis of 1,2-O-isopropylidene-α-D-ribofuranose (12):** The light-yellow oil 11 (7.60 g, 27.7 mmol) was dissolved in MeOH (60 mL). To the solution K2CO3 (0.60 g, 4.4 mmol) was added and the reaction mixture was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column to give 12 as a white solid (4.60 g, 93%). [α]D25 +42.3 (c 0.1, CH3OH) (lit. [38] [α]D25 +49 (c 0.94, CHCl3); 1H NMR (400 MHz, DMSO-d6) δ 5.65 (d, J = 3.7 Hz, 1H), 4.98 (d, J = 6.7 Hz, 1H), 4.64 (t, J = 5.6 Hz, 1H), 4.43 (t, J = 3.9 Hz, 1H), 3.79–3.56 (m, 3H), 3.41–3.35 (m, 1H), 1.43 (s, 3H), 1.26 (s, 3H); 13C NMR (101 MHz, DMSO-d6) δ 111.1, 103.3, 80.3, 79.1, 70.5, 60.2, 26.6, 26.4; LRMS (ESI) m/z: 213.3 [M + Na]+, 189.3 [M – H]; HRMS (ESI) m/z: [M + Na]+ cale for C6H13O2Na, 213.0733; found, 213.0731.

**Synthesis of 1,2-O-isopropylidene-5-O-(2-iodo benzoyl)-α-D-ribofuranose (13):** To a solution of 12 (6.60 g, 34.7 mmol) in dry CH2Cl2 (50 mL) and dry pyridine (7.62 mL) were added 0.2 mL 2-iodobenzoyl chloride (8.4 g, 31.5 mmol) at −10 °C under argon. After addition, the reaction mixture was stirred overnight and quenched with iced water (5 mL). The mixture was washed with sat. NaHCO3 (40 mL), brine (40 mL), and dried over anhydrous MgSO4. After filtration, the filtrated was evaporated to dryness under reduced pressure. The remaining residue was recrystallized by ethanol to obtain 13 as a white powder solid (10.7 g, 80%). [α]D25 +26.86 (c 0.18, CH3OH); 1H NMR (400 MHz, CDCl3) δ 7.99 (d, J = 8.0 Hz, 1H), 7.82 (dd, J = 7.8, 1.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.15 (td, J = 7.7, 1.6 Hz, 1H), 5.84 (d, J = 3.8 Hz, 1H), 4.70 (dd, J = 12.3, 2.5 Hz, 1H), 4.61 (t, J = 4.4 Hz 1H), 4.45 (dd, J = 12.3, 5.2 Hz, 1H), 4.11–4.07 (m, 1H), 3.98 (dd, J = 9.0, 5.1 Hz, 1H), 2.23 (brs, 1H), 1.58 (s, 3H), 1.37 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 166.4, 141.4, 134.8, 133.0, 131.4, 128.0, 113.0, 104.2, 94.3, 78.4, 78.3, 72.2, 64.1, 26.7, 26.6; LRMS (ESI) m/z: [M + Na]+ cale for C15H17IO6Na, 442.9967; found, 442.9980.

**Synthesis of 1,2-O-isopropylidene-5-O-(2-hex-1-yn-1-y) benzyol)-α-D-ribofuranose (14):** To a solution of 13 (9.0 g, 21.4 mmol) in dry Et3N (25 mL) and dry THF (50 mL) was added Cul (0.41 g, 2.1 mmol), PdCl2(PPh3)2 (2.07 g, 2.1 mmol) and 1-hexyne (2.68 mL, 23.5 mmol). After addition, the reaction mixture was heated at 50 °C for 1 h. TLC detection showed the reaction was finished. The reaction mixture was filtered over a bed of celite. After filtration, the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (PE/EtOAc 3:1; v:v) to afford 14 as deep green oil (6.35 g, 78%). [α]D25 +21.33 (c 0.15, CH3OH); 1H NMR (400 MHz,
DMSO-d$_6$ δ 7.81 (d, $J = 7.8$ Hz, 1H), 7.90–7.58 (m, 2H), 7.45 (td, $J = 7.2$, 2.0 Hz, 1H), 5.71 (d, $J = 3.6$ Hz, 1H), 5.34 (d, $J = 6.9$ Hz, 1H), 4.56–4.50 (m, 2H), 4.22 (dd, $J = 12.2$, 6.1 Hz, 1H), 4.05–4.01 (m, 1H), 3.86–3.81 (m, 1H), 2.45 (t, $J = 6.9$ Hz, 2H), 1.55–1.50 (m, 2H), 1.47–1.41 (m, 5H), 1.27 (s, 3H), 0.91 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 165.6, 133.8, 132.0, 131.9, 129.8, 127.8, 123.3, 111.5, 103.5, 95.9, 78.9, 78.8, 76.9, 71.3, 64.1, 30.1, 26.6, 26.3, 21.4, 18.6, 13.5; HRMS (ESI) m/z: [M + Na]$^+$ cale for C$_2$H$_{32}$O$_6$Na, 397.1627; found, 397.1608.

**Synthesis of 1,2-O-isopropylidene-3-O-(2,4-dimethoxy-6-methylbenzoyl)-5-O-(2-(hex-1-yn-1-yl)benzoyl)-D-ribofuranose (15):** To a solution of 14 (3.0 g, 8.0 mmol) in dry CH$_2$Cl$_2$ (25 mL) was added DMAP (97.88 mg, 0.8 mmol) and Et$_3$N (10.5 mg, 0.10 mmol). To the mixture benzoyl chloride 9 (2.15 g, 10 mmol) in dry CH$_2$Cl$_2$ (10 mL) was slowly added at 0 °C and stirred overnight at room temperature. The reaction was quenched with methanol (5 mL) and evaporated to dryness under reduced pressure. The obtained residue was dissolved in CH$_2$Cl$_2$ (40 mL), washed with sat. NaHCO$_3$ (40 mL × 2), brine (30 mL × 2), and dried over anhydrous MgSO$_4$. The obtained residue was purified by a silica gel column chromatography (PE/ EtOAc 4:1, v:v) to afford 15 as colorless oil (3.3 g, 74%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, $J = 7.8$ Hz, 1H), 7.49 (d, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 7.4$ Hz, 1H), 7.26 (t, $J = 7.6$ Hz, 1H), 6.30 (d, $J = 9.7$ Hz, 2H), 5.92 (d, $J = 3.7$ Hz, 1H), 5.03 (t, $J = 4.0$ Hz, 1H), 4.94 (dd, $J = 9.3$, 4.8 Hz, 1H), 4.69 (dd, $J = 12.2$, 2.4 Hz, 1H), 4.56–4.47 (m, 1H), 4.40 (dd, $J = 12.2$, 5.4 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.47 (t, $J = 7.0$ Hz, 2H), 2.35 (s, 3H), 1.63–1.57 (m, 2H), 1.55 (s, 3H), 1.47 (d, $J = 7.8$ Hz, 2H), 1.36 (s, 3H), 0.92 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.3, 166.0, 166.1, 138.2, 134.4, 134.7, 131.7, 131.3, 130.4, 127.1, 124.8, 115.1, 113.1, 110.6, 106.4, 96.6, 96.1, 79.1, 77.3, 75.6, 73.2, 63.4, 55.8, 55.4, 50.2, 26.7, 22.1, 20.1, 19.5, 13.7; HRMS (ESI) m/z: [M + Na]$^+$ cale for C$_{31}$H$_{36}$O$_{11}$Na, 619.2150; found, 619.2150.

**Synthesis of 1,2-O-diacyl-3-O-(2,4-dimethoxy-6-methylbenzoyl)-5-O-(2-(hex-1-yn-1-yl)benzoyl)-D-ribofuranosylo)uracil (17):** To a suspension of uracil (0.24 g, 2.2 mmol) in dry MeCN (15 mL) was added BSA (1.36 g, 6.7 mmol). The mixture was heated at 50 °C for 20 min. After cooled to room temperature, a solution of 16 (1.00 g, 1.7 mmol) in dry MeCN (5 mL) along with TMSOTf (1.30 g, 5.9 mmol) were added to the above reaction mixture at 0 °C. The solution was stirred for 5 min before heating to 75 °C for 3–4 h. Then the reaction mixture was poured into cold sat. NaHCO$_3$ solution (30 mL). It was extracted with CH$_2$Cl$_2$ (50 mL). The combined organic layer was washed with sat. aq NaHCO$_3$ (100 mL × 2), brine (50 mL × 2), and dried with anhydrous Na$_2$SO$_4$. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/CH$_3$OH, 10:1) to give nucleoside 17 as a white solid (0.96 g, 89%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.53 (s, 1H), 7.78 (d, $J = 7.4$ Hz, 1H), 7.56 (d, $J = 7.4$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.30–7.33 (m, 2H), 6.33 (s, 2H), 6.19 (d, $J = 6.1$ Hz, 1H), 5.67–5.64 (m, 1H), 5.52 (dd, $J = 8.1$, 1H), 5.42 (t, $J = 5.9$ Hz, 1H), 4.72 (dd, $J = 12.4$, 2.5 Hz, 1H), 4.64 (dd, $J =$
12.4, 3.1 Hz, 1H'), 4.58–4.55 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.46 (t, J = 7.0 Hz, 2H), 2.32 (s, 3H), 2.05 (s, 3H), 1.63–1.55 (m, 2H), 1.51–1.41 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 169.7, 166.9, 166.0, 163.1, 162.1, 159.1, 150.5, 139.3, 134.5, 132.2, 131.4, 129.8, 127.6, 124.6, 114.4, 107.1 103.4, 96.8, 96.4, 86.7, 80.6, 78.9, 73.0, 71.1, 63.8, 56.0, 55.5, 30.7, 22.1, 20.6, 20.2, 19.5, 13.7; HRMS (ESI) m/z: [M + Na]+ caked for C34H36N2O11Na, 671.2217; found, 671.2214.

Synthesis of kipukasin A: To a solution of nucleoside 17 (0.60 g, 0.92 mmol) in dry CH2Cl2 (15 mL) was added H2O (1.0 equiv) and ethanol (6.0 equiv) under an argon atmosphere. The mixture was stirred at room temperature for 20 minutes. A freshly prepared solution of Ph3PdAuOTf in CH2Cl2 (5 mol % in 1.0 mL) was added, and stirring was continued at room temperature for 5 hours until nucleoside 17 was consumed as monitored by TLC. The reaction mixture was filtered with celite. After filtration, the filtrate was evaporated to dryness under reduced pressure. The obtained residue was recrystallized in petroleum ether (5 mL) to provide kipukasin A as a white powder solid (387 mg, 90%). 

Supporting Information
Supporting Information File 1
Experimental procedures of compounds 6–9, copies of 1H and 13C NMR spectra of all compounds and X-ray crystal data of compound 13.

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