Arabian Journal of Chemistry (2016) 9, S1597–S1602

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

A synthesis of (±)-thia-calanolide A, its resolution and in vitro biological evaluation

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Received 22 July 2011; accepted 21 April 2012
Available online 2 May 2012

KEYWORDS

Thiocoumarin;
Thia-calanolide A;
Anti-HIV activity;
Resolution via chiral HPLC

Abstract A synthesis of (±)-thia-calanolide A **3** has been successfully accomplished starting from 3,5-dimethoxythiophenol **4**, in six steps in an overall yield of 4.5%. The key reaction involved Friedel–Crafts tigloylation of 5,7-dihydroxy-4-*n*-propyl thiocoumarin **6** employing an appropriate solvent of CS_2–$PhNO_2$ in a ratio of 7:3. In its biological evaluation for anti-HIV activity, (±)-thia-calanolide A **3** demonstrated comparatively less activity with calanolide A and its synthetic analogue aza-calanolide. Further, (±)-3 has been resolved by chiral HPLC to (+) and (−)-**3**.

1. Introduction

(+)-Calanolide A [(+)-**1**], non-nucleoside reverse transcriptase inhibitor (NNRTI) and few new coumarin derivatives isolated from *Calophyllum langerum* (Kashman et al., 1992) which showed promising activity towards human immunodeficiency virus (HIV-1) reverse transcriptase (Currens et al., 1996a,b). It is also active against many strains of *Mycobacterium tuberculosis* including those resistant to the standard antitubercular drugs (Xu et al., 2004) and is reported through molecular dynamics simulation of SARS-CoV to be a potent proteinase inhibitor (Lee et al., 2003). Calanolide A is in clinical testing phase II as anti-HIV drug; (Buckheit et al., 2000; Cragg and Newman, 2003) interest therefore arose particularly in developing its analogues. So far, most of the analogues were either less potent or devoid of any anti-HIV activity (Galinis et al., 1996; Zhou et al., 1999; Zembower et al., 1997; Xu et al., 1998; Newman et al., 1998); however, aza-calanolide A [(±)-**2**] (Sharma et al., 2003) exhibited enhanced in vitro anti-HIV reverse transcriptase activity. These findings prompted us to undertake the total synthesis of thia-calanolide A **3** by replacing oxygen in ring B with a sulphur atom, which might exhibit better activity. Herein, we describe the first synthesis, optical resolution and in vitro biological evaluation of (±)thia-calanolide A **3** (Fig. 1).

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2012.04.027

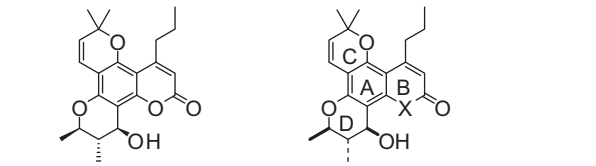
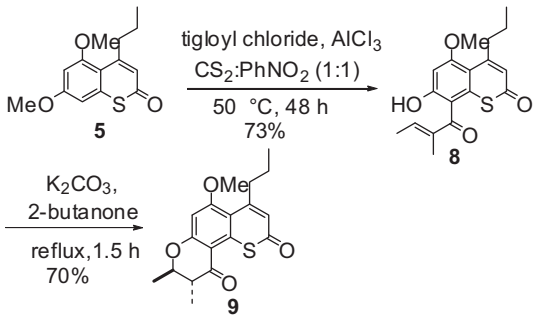


Figure 1 Structure of **1**, **2**, **3**.

2. Results and discussion

Thiophenol **4**, obtained from phloroglucinol (Wolfers et al., 1975) or from 3,5-dimethoxyaniline by diazotization followed by reaction with $Na_2S + S$ or NaSH (Allen and Mackay, 1943) was subjected to Pechmann condensation with ethylbutyrylacetate in presence of sulphuric acid (Sethna and Phadke, 1953). However, it yielded the undesired 7-hydroxy-5-methoxy-2-propyl-4*H*-thiochromen-4-one. The required 5,7-dimethoxy-4-propyl-2*H*-thiochromen-2-one **5** was obtained by a modified Pechmann method where triflic acid was used instead of H_2SO_4. Demethylation with $AlCl_3$ yielded 5,7-dihydroxythiocoumarin **6**. Friedel–Crafts acylation (Olah, 1964) of **6** with tigloyl chloride yielded a 3:1 mixture of 5,7-ditigloyloxy thiocoumarin **7a** and 5-hydroxy-7-tigloyloxy thiocoumarin **7b** instead of the required C-8 tigloyl coumarin **7** (Scheme 1).

In an alternate route (Sekino et al., 2004) thiocoumarin **5** was subjected to Friedel–Crafts reaction with tigloylchloride to yield 5-methoxy-7-hydroxy-8-tigloylthiacoumarin **8**. Intramolecular oxo-Michael addition (IMA) of the latter furnished the chromanone **9**. Subsequent demethylation of **9** with various reagents like BBr_3/CH_2Cl_2 at −70 °C (Vickery et al., 1979), BBr_3-SMe_2/CH_2Cl_2 (Williard and Fryhle, 1980), BF_3-Et_2O/CH_2Cl_2 (Preston et al., 1983), $AlCl_3$/PhCl at 120 °C (Chenera et al., 1993), and MgI_2/K_2CO_3/PhH (Sekino et al., 2004) under reflux for 15 days did not proceed satisfactorily to yield the expected demethylated product. With BBr_3/CH_2Cl_2, compound **8** was regenerated, whereas the starting thiocoumarin **9** was recovered unchanged with other reagents (Scheme 2).

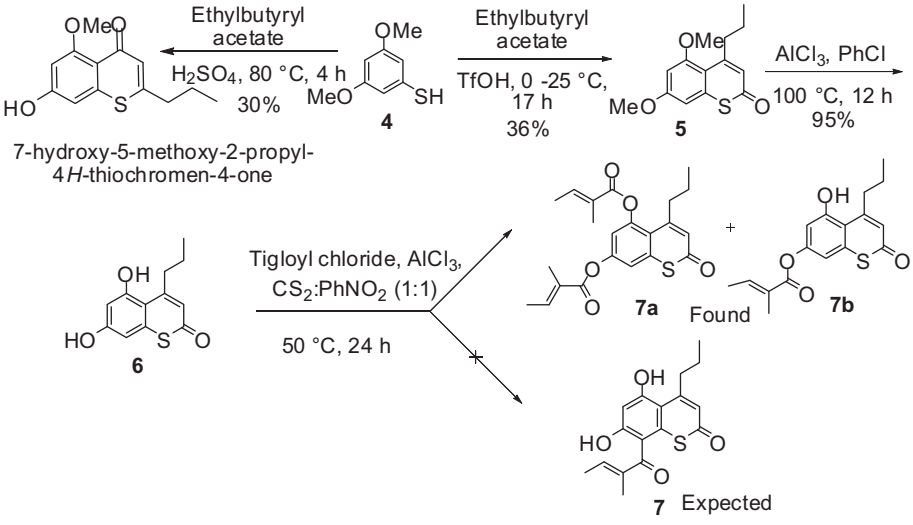


Scheme 2

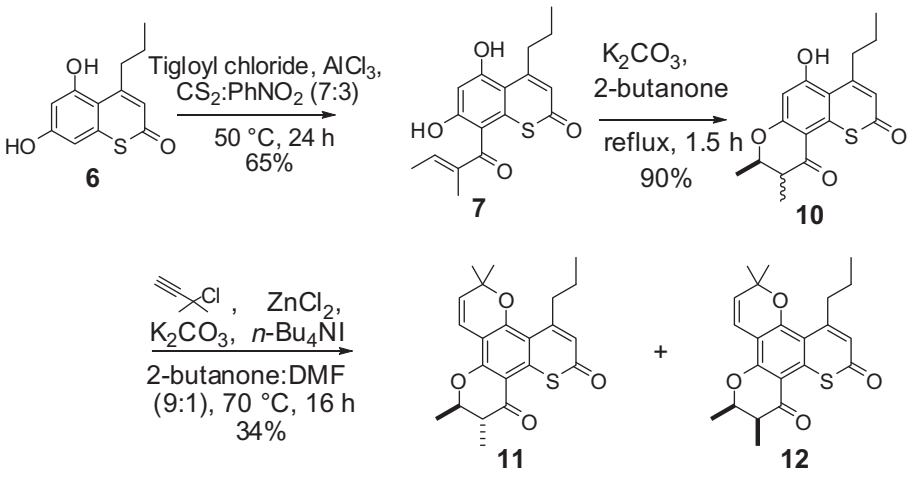
Successful tigloylation was achieved via Friedel–Crafts reaction from compound **6** employing an appropriate solvent in a ratio CS_2–$PhNO_2$ (7:3). The product **7** thus formed was cyclized with K_2CO_3 yielded the desired 8,9-dimethyldihydrothiopyranones **10** as an 1:1 epimeric mixture. The required 'C' ring was constructed from **10** by reaction with 3-chloro-3-methyl-1-butyne to yield chromene-chromanone–thiacoumarins 11 and **12** in a 1.8:1 ratio and in an overall yield of 34% (Scheme 3).

Both the ketones **11** and **12** were separately reduced with $NaBH_4$ to afford (±)-**3** and (±)-thia-calanolide C **14** in 44% and 71% yields, respectively. Reduction of **11** with $NaBH_4$–$CeCl_3$ under Luche condition resulted in a 3:2 mixture of (±)-**3** and (±)-thia-calanolide B (±)-**13**, respectively (Scheme 4).

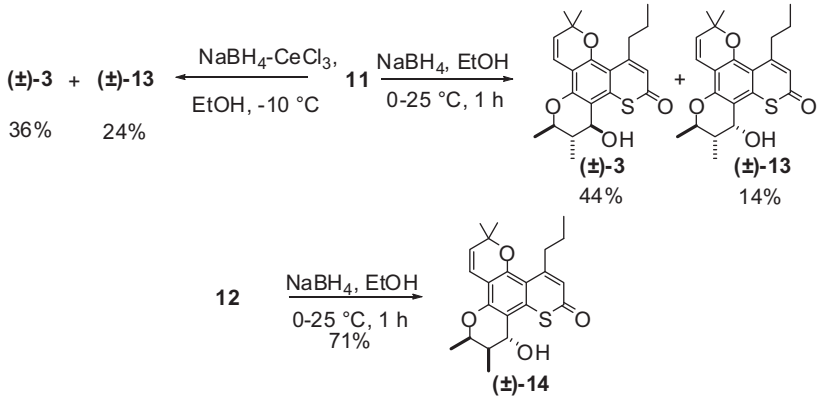
For the first time, in the calanolide series, especially in the thia-calanolide A synthesis, application of HPLC method for determination and separation of small quantities of the intermediates in the total synthesis of (+)-thia-calanolide has been developed. Resolution of a mixture of *cis* and *trans* of **10** was found to be excellent using Bondapak silica porasil 30 cm column.



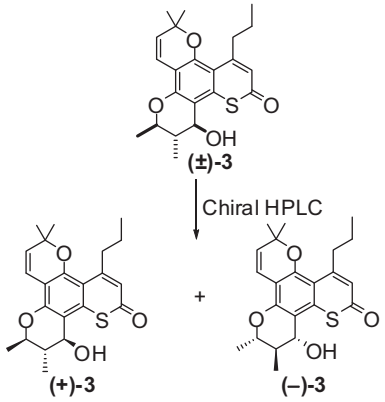
Scheme 1



Scheme 3



Scheme 4



Scheme 5

Resolution of (±)-**3** was achieved by chiral HPLC (Chiralcel (OD), 9:1 hexane–isopropanol, 1 mL/min) to afford the two isomers (+)-**3** and (–)-**3** having optical rotation $[\alpha]_D$ + 54.3° (*c* 0.5, $CHCl_3$) and $[\alpha]_D$ −49.8° (*c* 0.3, $CHCl_3$), respectively (Scheme 5).

2.1. Anti-HIV activity assays

Compound (±)-**3** was evaluated for anti-HIV reverse transcriptase activity by following HIV-1 p24 antigen capture ELISA (Perkin Elmer NEN) as per manufacturer's protocol. Briefly, CEM cells were infected with HIV-1 NL4.3 isolate for 4 h in presence of Poltbrene in complete medium. The infected cells were kept for 7–10 days in culture before the supernatant was used for HIV-1 p24 antigen capture. The percentage inhibition of virus production was calculated based on p24 values of untreated control. (±)-**3** was found to be 28% inhibitory as compared to synthetic (±)-**1** which was found to exhibit 99.7% inhibition of virus production.

3. Conclusion

The first synthesis of (±)-thia-calanolide **3** has been successfully accomplished. It has also been resolved by chiral HPLC to the (+) and (–) enantiomers which have been fully characterized. Biological evaluation for anti-HIV activity revealed that **3** is not as achieved as the natural calanolide A and its synthetic analogue aza-calanolide A. The amphoteric and

bulkier nature of sulphur in **3** could be one of the reasons for diminished activity.

4. Experimental section

4.1. General

NMR spectra were recorded on a Bruker MSL-300 spectrometer operation at 300 MHz for ^{1}H and 75 MHz for ^{13}C and Bruker AV-200 spectrometer operation at 200 MHz for ^{1}H and 50 MHz for ^{13}C. Spectra were obtained at 25 °C in $CDCl_3$, DMSO-d_6 and Acetone-d_6 solution and were referenced to the $CHCl_3$ peak (δ 7.26), DMSO (δ 2.50) for ^{1}H or to the center line of the $CDCl_3$, DMSO-d_6, acetone-d_6 at δ 77, 39.70, 29.8, respectively, for ^{13}C, all chemical shifts are given as δ values (in ppm) relative to TMS. IR spectra were recorded on Perkin-Elmer FT IR instrument. Optical rotations were measured as $CHCl_3$ solution using Jasco P-1020 digital polarimeter. Microanalyses were performed on a Flash EA-1112 Thermo Finnigan Elemental Analyser. Chiral HPLC was performed on a SHIMADZU Class-VP using a Chiracel OD column. Melting points were determined by using a Yanco Micro Melting point apparatus and were uncorrected.

Reactions with moisture-sensitive chemicals were performed under nitrogen in flame-dried reaction flasks. Solvents were dried by standard methods. Column chromatography was carried out using 60–80 mesh and 230–400 mesh silica gel. Phloroglucinol, dimethylthiocarbamoyl chloride, trifluoromethanesulfonic acid, ethyl butyrylacetate, tiglic acid, 3-chloro-3-methyl-1-butyne were purchased from Aldrich and were used without purification.

*4.1.1. 5,7-Dimethoxy-4-n-propyl-2H-thiochromen-2-one (**5**)*

A mixture of **4** (0.540 g, 3.17 mmol) and ethylbutyrylacetate (0.527 g, 3.3 mmol) was added dropwise to cold (5 °C) trifluoromethanesulfonic acid (0.55 mL, 6.34 mmol) over a 10 min period and the reaction mixture was warmed to 25 °C and stirred for 17 h. After quenching with ice water (10 mL), the mixture was extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine (2×10 mL), dried (Na_2SO_4) and concentrated. The residue was subjected to chromatographic purification (EtOAc–pet-ether, 2:8) to give **5** as lemon yellow crystals (0.301 g, 36%). Mp 110–112 °C, IR ($CHCl_3$) 3016, 2965, 1630, 1593 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.58 (m, 2H), 2.90 (t, J = 7.3 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 6.20 (s, 1H), 6.37 (d, J = 2.5 Hz, 1H), 6.49 (d, J = 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 24.0, 41.8, 55.5, 55.6, 98.2, 101.8, 111.5, 122.7, 142.4, 156.9, 160.7, 160.8, 184.1. Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10; S, 12.13. Found: C, 63.61; H, 6.21; S, 11.07.

*4.1.2. 5,7-Dihydroxy-4-n-propyl-2H-thiochromen-2-one (**6**)*

To a stirred solution of **5** (1 g, 3.78 mmol) in chlorobenzene (10 mL) was added $AlCl_3$ (2.5 g, 1.89 mmol) in portions over a period of 15 min and the reaction mixture was heated to 100 °C under stirring for 12 h. The mixture was then cooled to room temperature and poured on crushed ice (20 g) and stirred well for 30 min. The solid precipitated was filtered, washed with water (50 mL) till neutral, then washed with hexane (5 mL) and dried in vacuum to give 6 (0.849 g, 95%) as a dark brown solid. Mp 230–235 °C (decomp.): IR ($CHCl_3$) 3159, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 0.95 (t, J = 7.3 Hz, 3H), 1.60 (m, 2H), 2.97 (t, J = 7.3 Hz, 2H), 6.04 (s, 1H), 6.39 (s, 2H), 9.70 (s, 1H), 10.02 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.0, 24.0, 40.7, 102.6, 104.4, 108.2, 120.3, 140.9, 158.1, 159.7, 159.9, 182.6; Anal. Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57. Found: C, 60.75; H, 4.98; S, 12.38.

4.1.3. (E)-5,7-Dihydroxy-8-(2-methylbut-2-enoyl)-4-n-propyl-2H-thiochromen-2-one (7)

A mixture of **6** (0.5 g, 2.11 mmol), $AlCl_3$ (1.4 g, 10.59 mmol) and CS_2 (7 mL) was heated at 50 °C while stirring for 30 min $PhNO_2$ (2 mL) was added dropwise and stirred for additional 30 min to get a homogeneous mixture. Tigloyl chloride (0.262 g, 2.21 mmol) in $PhNO_2$ (1 mL) was then added dropwise and the reaction mixture was stirred at 50 °C for 24 h. It was then cooled to room temperature and quenched with crushed ice and dil. HCl before extracting with EtOAc (3×30 mL). The combined organic layer was washed with brine (3×20 mL), dried (Na_2SO_4) and concentrated. The residue obtained was purified by column chromatography on silica gel (EtOAc–pet-ether, 4:6) to furnish **7** (0.437 g, 65%) as a brown solid. Mp 162–164 °C: IR ($CHCl_3$) 3263, 3019, 1720, 1610 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.99 (t, J = 7.2 Hz, 3H), 1.62 (m, 2H), 1.84 (d, J = 7.0 Hz, 3H), 1.87 (s, 3H), 3.04 (t, J = 7.5 Hz, 2H), 6.17 (s, 1H), 6.49 (q, J = 7.0 Hz, 1H), 6.64 (s, 1H), 10.69 (s, 1H), 11.03 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 10.5, 14.0, 14.9, 24.1, 41.1, 102.1, 107.9, 117.4, 120.1, 137.9, 138.1, 142.4, 156.7, 158.4, 159.9, 181.6, 196.2; Anal. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70; S, 10.07. Found: C, 63.65; H, 5.58; S, 9.53.

*4.1.4. 5-Hydroxy-8,9-dimethyl-4-n-propyl-8,9-dihydrothiopyrano[2,3-f]chromene-2,10-dione (**10**)*

To a solution of **7** (0.4 g, 1.25 mmol) in 2-butanone (5 mL), anhydrous K_2CO_3 (0.520 g, 3.77 mmol) was added and the mixture was refluxed for 1.5 h. It was then cooled to room temperature, acidified (pH 2) with dil. HCl and extracted with EtOAc (3×20 mL). The combined organic layer was washed with brine (3×10 mL), dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel column (EtOAc–pet-ether, 3:7) to give a 1:1 mixture of isomeric chromanones 10 (0.360 g, 90%) as white solid, mp 243–245 °C: IR (Nujol) 3130, 3020, 1621 cm^{-1}; Anal. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70; S, 10.07. Found: C, 63.86; H, 5.72; S, 9.05.

*4.1.5. 6,7-Dihydro-2H-1,5-dioxa-12-n-propyl-2,2,6,7-tetramethyl-9-thia-triphenylene-8,10-dione (**11** trans and **12** cis)*

To a stirred solution of **10** (0.5 g, 1.57 mmol) in a mixture containing 2-butanone: DMF (10 mL, 9:1), at room temperature, anhydrous K_2CO_3 (0.65 g, 4.71 mmol), 3-chloro-3-methyl-1-butyne (0.8 g, 7.85 mmol), n-Bu_4NI (0.49 g, 1.22 mmol) were added successively. The reaction mixture was heated at 60 °C for 1 h, and then anhydrous $ZnCl_2$ (0.278 g, 2.04 mmol) was added. The resultant mixture was further heated to 70 °C for 20 h. It was cooled to room temperature and quenched with saturated aq. solution of NH_4Cl (3 mL) and extracted with EtOAc (2×30 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The residue obtained was purified through column chromatography

on silica gel (230–400 mesh, EtOAc–pet-ether, 1:9) to afford (±)-**11** (0.132 g, 22%) as a white solid. Mp 143–144 °C: IR ($CHCl_3$) 1670, 1627, 1201 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H), 1.53 (d, J = 6.5 Hz, 3H), 1.58 (s, 6H), 1.67 (m, 2H), 2.60 (m, J = 6.8, 11.5 Hz, 1H), 2.98 (t, J = 7.2 Hz, 2H), 4.28 (dq, J = 6.3, 11.5 Hz, 1H), 5.64 (d, J = 10.1 Hz, 1H), 6.37 (s, 1H), 6.67 (d, J = 10.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.2, 13.9, 19.5, 24.2, 27.7, 28.1, 42.0, 46.5, 78.8, 79.4, 107.5, 109.0, 112.9, 115.8, 123.9, 128.0, 143.9, 156.0, 158.3, 158.8, 186.3, 192.5; Anal. Calcd for $C_{22}H_{24}O_4S$: C, 68.72; H, 6.29; S, 8.34. Found: C, 68.36; H, 6.32; S, 7.99; and (±)-thia-calanolide D (±)-**12** (0.072 g, 12%) as a syrup liquid; IR ($CHCl_3$) 1670, 1627, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ1.02 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 7.3 Hz, 3H), 1.43 (d, J = 5.8 Hz, 3H), 1.56 (s, 6H), 1.64 (m, 2H), 2.70–2.75 (m, J = 3.6, 7.3 Hz, 1H), 2.96 (t, J = 7.2 Hz, 2H), 4.70 (m, J = 2.9, 6.6 Hz, 1H), 5.65 (d, J = 9.5 Hz, 1H), 6.39 (d, 1H), 6.69 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 13.9, 19.5, 24.3, 27.9, 28.2, 42.0, 46.7, 77.7, 78.9, 79.4, 96.1, 107.5, 116.0, 124.1, 127.9, 144.4, 155.7, 158.1, 158.8, 186.0, 192.1; Anal. Calcd for $C_{22}H_{24}O_4S$: C, 68.72; H, 6.29; S, 8.30. Found: C, 68.88; H, 6.33; S, 8. 29.

*4.1.6. (±)-6,7-Dihydro-2H-1,5-dioxa-8-hydroxy-12-n-propyl-2,2,6,7-tetramethyl-9-thia-triphenylene-10-one (**3**, **13**)*

To a solution of (±)-**11** (0.020 g, 0.052 mmol) in EtOH (2 mL) at 0 °C, was added $NaBH_4$ (0.003 g, 0.083 mmol) and the reaction temperature was allowed to rise to 25 °C over a period of 1 h. After completion of the reaction 2–3 drops of water were added and the reaction mixture was extracted with EtOAC (3 × 3 mL), the combined organic layer was washed with brine, dried with Na_2SO_4 and concentrated. The residue obtained was purified through flash column chromatography (EtOAc–pet-ether, 2:8) to give (±)-thia-calanolide A (±)-**3** (0.009 g, 44%) as a white solid. Mp 158–160 °C: IR ($CHCl_3$) 3410, 1619, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 1.12 (d, J = 7 Hz, 3H), 1.48 (d, J = 6.8 Hz, 3H), 1.52 (s, 6H), 1.64 (m, 2H), 2.05 (sext, J = 6, 13.4 Hz, 1H), 3.01 (dq, 3.4, 8.0, 2H), 4.02 (quin, J = 6.6, 13.1 Hz, 1H), 4.55 (d, J = 5.9 Hz, 1H), 5.60 (d, J = 9.9 Hz, 1H,), 6.3 (s, 1H), 6.66 (d, J = 9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ 14.0, 15.9, 19.2, 24.5, 27.5, 27.9, 41.7, 42.1, 68.2, 77.8, 108.9, 112.0, 112.7, 116.8, 122.5, 128.0, 140.9, 151.5, 153.3, 157.9, 183.6; ^{13}C NMR (75 MHz, Acetone-d_6) δ 14.5, 15.9, 19.7, 25.6, 27.7, 28.3, 42.8, 43.6, 69.0, 77.7, 78.8, 109.7, 112.5, 115.0, 117.6, 123.4, 129.4, 142.5, 153.7, 154.0, 157.9, 184.2. Anal. Calcd for $C_{22}H_{26}O_4S$: C, 68.37; H, 6.78; S, 8.30. Found: C, 68.81; H, 6.87; S, 8.03; and (±)-thia-calanolide B (±)-**13** (0.003 g, 14%) as a white solid mp 156–158 °C: IR ($CHCl_3$) 3400, 1621, 1533, 1122 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H), 1.41 (d, J = 6.3 Hz, 3H), 1.49 (s, 6H), 1.65 (m, 2H), 2.30 (m, J = 5.8,12.7 Hz, 1H), 3.01 (m, 2H), 4.49 (m, J = 6.8, 13.7 Hz, 1H), 4.82 (d, J = 6 Hz, 1H), 5.63 (d, J = 9.8 Hz, 1H), 6.31 (s, 1H), 6.70 (d, J = 9.8 Hz, 1H).

*4.1.7. (±)-6,7-Dihydro-2H-1,5-dioxa-8-hydroxy-12-n- propyl-2,2,6,7-tetramethyl-9-thia-triphenylene-10-one (**14**)*

To a solution of 12 (0.050 g, 0.13 mmol) in EtOH (5 mL) at 0 °C was added $NaBH_4$ (0.009 g, 0.26 mmol) while stirring and the temperature was allowed to rise to 30 °C and the mixture was stirred further for 1 h. After completion of reaction, ice water (1 mL) was added and the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried (Na_2SO_4) and concentrated. The residue obtained was purified through flash column chromatography on silica gel (230–400 mesh, EtOAc–pet-ether, 2:8) to give (±)-**14** (0.036 g, 71%) as a white solid. Mp 167–168 °C: IR ($CHCl_3$) 3400, 1619, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 1.21 (d, J = 7.3 Hz, 3H), 1.53 (d, J = 6.5 Hz, 3H), 1.55 (s, 3H), 1.58 (s, 6H), 1.67 (m, 2H), 2.62 (m, 1H), 3.46 (m, 2H), 4.28 (m, J = 2.2, 6.6 Hz, 1H), 4.79 (d, J = 3.6 Hz, 1H), 5.67 (d, J = 9.5 Hz, 1H), 6.37 (d, 1H), 6.70 (d, J = 9.5 Hz, 1H). Anal. Calcd for $C_{22}H_{26}O_4S$: C, 68.37; H, 6.78; S, 8.30. Found: C, 68.65; H, 6.91; S, 8.44.

Acknowledgments

A.U.C. thank UGC-CSIR, New Delhi, for the award of a research fellowship. NCCS (Pune) is thanked for anti-HIV activity assays.

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