Potent Activity against Multidrug-Resistant *Mycobacterium tuberculosis* of *α*-Mangostin Analogs

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A new series of mangostin analogs of natural *α*-mangostin from mangosteen was prepared and their antimycobacterial activity was evaluated *in vitro* against *Mycobacterium tuberculosis* H_{37}Ra. The results showed that the monoalkyl tetrahydro *α*-mangostin analogs displayed increased antimycobacterial activity as compared with the lead natural xanthone, *α*-mangostin. Among the tested compounds, 6-methoxytetrahydro *α*-mangostin (16) exhibited the most potent antimycobacterial activity with minimum inhibitory concentration (MIC) of 0.78 *μ*g/mL. The activity of the monoalkylated and monoacylated tetrahydro *α*-mangostins decreases as the length of carbon chain increases. The methyl ether analog was also active against the multidrug-resistant (MDR) strains with pronounced MICs of 0.78–1.56 *μ*g/mL.

Key words mangostin analog; chemical modification; anti-tuberculosis activity

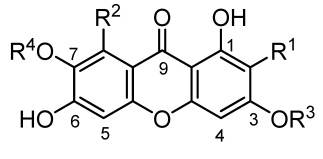
Tuberculosis (TB) remains a currently serious problem worldwide due to the rapid spread of TB strains resistant to all the major anti-tuberculosis drugs on the market, and the association of TB with the human immunodeficiency virus (HIV) leading to infection and death.[1)] Nearly 2 million die from it and more than 9 million people per annum are infected.[2)] It is now generally accepted that new drugs to cure TB are urgently needed due to the recent increment of multidrug-resistant mycobacteria. The drug discovery based on structure modification of natural products is a challenging strategy for new antitubercular drugs which are different from the drugs currently used. In this regard, the naturally occurring bioactive molecules constitute ideal starting material templates and natural-product like libraries synthesis in particular is of increasing interest.[3,4)]

Prenylated xanthones, secondary metabolites from higher plants, display a wide spectrum of biological profiles[5–7)] such as antioxidant,[8)] antiinflammatory,[9)] hepatoprotective,[10)] cancer preventive,[11)] antimalarial[12)] and antibacterial activities,[13)] based on their diverse structures. *α*-, *β*- and *γ*-Mangostins (**1**–**3**), the major prenylated xanthones of *Garcinia mangoatana* L.[14)] and some other *Garcinia* plants,[6)] revealed interesting antimycobacterial potential against *Mycobacterium tuberculosis* at the respective minimal inhibitory concentrations (MICs) of 6.25, 6.25 and 50 *μ*g/mL.[15)] Our preliminary study on antimycobacterial xanthones of *G. mangostana* showed that the most active compounds were those oxygenated in the 1,3,6,7-positions and prenylated in the 2 and 8-positions and together with the 1-hydroxyl and 7-methoxyl groups on the xanthone nucleus. In addition, increase in hydrophilicity at the prenyl side chain in garcinone D (**4**) and mangostenol (**5**), structures of which relate with *α*-mangostin (**1**), decreased the activity with MICs of 25 and 100 *μ*g/mL, respectively.[15)] In order to investigate structural requirements for antituberculosis activity of mangostin, we were interested in exploiting the 1-, 3- and 6-positions in the hydroxyl moieties and the isopentenyl moiety of *α*-mangostin as an extended structure activity relationship (SAR) study. The present paper deals with a new series of *O*-alkyl ethers and *O*-acyl analogs of *α*-mangostin and the tetrahydro *α*-mangostin and evaluation of the *in vitro* antimycobacterial activity.

Results and Discussion

Chemistry The synthetic strategy was to first prepare certain alkylated and acylated analogs (**6**–**14**) of *α*-mangostin (**1**), subsequently tetrahydro *α*-mangostin (**15**) and its methylated and demethylated derivatives (**16**–**23**), followed by the targeted analogs **24**–**48** to study the effects of free hydroxyl group and the analogs bearing side chains with different groups of the oxygen function at the aromatic rings on the xanthone nucleus.

Treatment of **1**, the most abundant xanthone of *G. mangostana* fruit, with alkylating or acylating agents under standard procedures gave the 6-mono- (**6**, **8**, **11**, **13**) and 3,6-di-*O*-substituted products (**7**, **10**, **12**, **14**) in 6–38% yield (Chart 1). In order to have the 3-mono- derivative for testing, the 3-*O*-ethyl *α*-mangostin (**9**) was prepared in 10% yield by reacting **1** with diethyl sulfate under dilution condition (see



1 $R^1 = R^2 =$  , R^3 = H, R^4 = Me

2 $R^1 = R^2 =$  , $R^3 = R^4$ = Me

3 $R^1 = R^2 =$  , $R^3 = R^4$ = H

4 $R^1 =$  , $R^2 =$  , R^3 = H, R^4 = Me

5 $R^1 =$  , $R^2 =$  , R^3 = H, R^4 = Me

Fig. 1. Prenylated Xanthones **1**–**5** of *G. mangostana*

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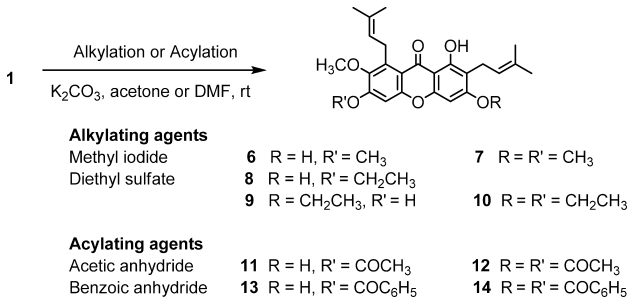


Chart 1. Alkylation and Acylation Reactions of α-Mangostin (**1**)

Experimental). Spectroscopic data of **8**, **9**, **11** and **14** were in agreement with the structures and those of compounds **6**, **7**, **10**, and **12** were consistent with the literature values.[16,17]

As shown in Chart 2, tetrahydro α-mangostin (**15**) was prepared in 98% from **1** by catalytic hydrogenation, which served as starting material for the synthesis of tetrahydro α-mangostin analogs. Compound **15** has previously been synthesized, however, its NMR data has not yet been presented.[18] The presence of two isopentyl resonances at C-2 and C-8 in its NMR data was consistent with the structure of **15**. The xanthone analogs **16**–**23** with varying numbers and positions of methoxyl groups were successfully synthesized. Methylation of **15** with methyl iodide–K_2CO_3 yielded the 6-mono- and 3,6-di-methylated products **16** and **17**. The 3-*O*-methyl ether **18** was obtained as a single product in 10% yield from compound **17**, by employing a modified procedure described previously,[19] *via* demethylation reaction in the presence of morpholine at 140°C. Prolonged heating of **17** at higher temperature furnished tetrahydro γ-mangostin (**19**) and 3-*O*-methyltetrahydro γ-mangostin (**20**) in 20 and 14% yields, respectively. Subsequently, methylation of **19** with excess methyl iodide at 5–10°C for 12 h in acetone catalyzed by potassium carbonate yielded 6-*O*-methyl- (**21**) (12%), 3,6-di-*O*-methyltetrahydro γ-mangostin (**22**) (47%) together with the fully methylated product **17**. Attempts to prepare the 1-*O*-methyl ether **23** by reacting the 3,6-di-*O*-acetate of **15** with CH_3I/K_2CO_3, however, resulted in partial ester hydrolysis prior to methylation at the 1-position. Nevertheless, compound **23** was obtained in 62% total yield by reacting **15** with tosyl chloride in the presence of potassium carbonate to give **23a**, followed by methylation with CH_3I–K_2CO_3 and deprotection of the tosylated intermediate **23b** with ethanolic potassium hydroxide solution. The absence of a down field hydrogen bonded signal and the presence of an additional methoxyl resonance at δ 3.85 in the ^{1}H-NMR spectrum confirmed the structure of **23**. The observed heteronuclear multiple bond correlations (HMBC) between the OCH_3 with their corresponding carbons in HMBC experiments further confirmed the structures for **15**–**23**.

A series of tetrahydro α-mangostin derivatives containing higher alkyl ether and ester analogs was prepared from **15** as indicated in Chart 3. Firstly, the corresponding 6-*O*-alkyl (**24**, **27**, **29**, **31**, **34**, **36**, **38**, **39**) and 3,6-di-*O*-alkyl ethers (**26**, **28**, **30**, **32**, **35**, **37**, **40**) were synthesized by treating **15** with different alkylating agents in a similar manner to the methylation method. Catalytic hydrogenation of allyl ether **31** yielded its saturated analog **33** in quantitative yield. In a like manner, the corresponding 6-*O*-monoester and 3,6-di-*O*-esters (**41**, **43**, **45**–**48**) were synthesized by reacting **15** with different carboxylic acid anhydride or acid halides under base-catalyzed conditions. Similarly, acetylation of **16** with acetic anhydride–K_2CO_3 led to the 3-OAc–6-OCH_3 substituted product **44** in 72% yield. The isomeric 3-*O*-ethyl ether **25** and 3-*O*-acetate **42** were obtained in 4 and 32% yields, respectively, from **15** in a similar dilute reaction condition procedure as for compound **9**. All synthetic compounds gave satisfactory spectroscopic data (1D- and 2D-NMR and MS).

Antituberculosis Evaluation The *in vitro* antituberculosis activity against *Mycobacterium tuberculosis* H_{37}Ra of mangostin analogs **6**–**48** by Alamar blue assay[20] were assessed, with kanamycin, isoniazid and rifampin as positive controls, and the MIC values are reported in Table 1. The 6-*O*-alkyl ethers **6** and **8** and the 6-*O*-esters **11** and **13** showed comparable activity (MICs 6.25–12.5 μg/mL) to the reported

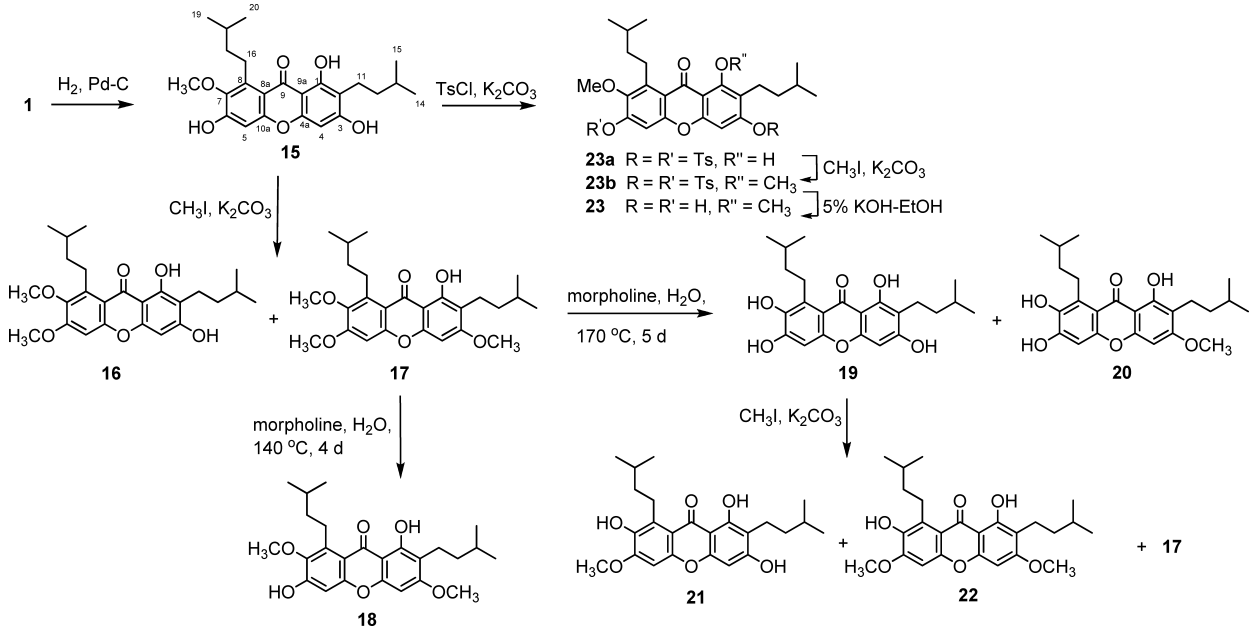
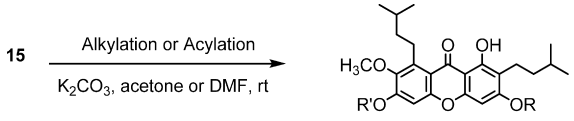


Chart 2. Synthesis of Tetrahydro α-Mangostin Analogs **15**–**23**



Alkylating agents

Diethyl sulfate	**24** R = H, R' = CH_2CH_3	
	25 R = CH_2CH_3, R' = H	**26** R = R' = CH_2CH_3
Bromo ethanol	**27** R = H, R' = CH_2CH_2OH	**28** R = R' = CH_2CH_2OH
Chloro acetamide	**29** R = H, R' = CH_2CONH_2	**30** R = R' = CH_2CONH_2
Allyl bromide	**31** R = H, R' = $CH_2CH=CH_2$] a	**32** R = R' = $CH_2CH=CH_2$
	33 R = H, R' = $CH_2CH_2CH_3$ ◄ a	
1-Bromobutane	**34** R = H, R' = $(CH_2)_3CH_3$	**35** R = R' = $(CH_2)_3CH_3$
1,4-Dibromobutane	**36** R = H, R' = $(CH_2)_4Br$	**37** R = R' = $(CH_2)_4Br$
1-Bromopentane	**38** R = H, R' = $(CH_2)_4CH_3$	
Benzyl bromide	**39** R = H, R' = $CH_2C_6H_5$	**40** R = R' = $CH_2C_6H_5$

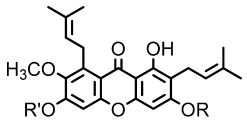
Acylating agents

Acetic anhydride	**41** R = H, R' = $COCH_3$	
	42 R = $COCH_3$, R' = H	**43** R = R' = $COCH_3$
	44 R = $COCH_3$, R' = CH_3	
Propionic anhydride	**45** R = R' = $COCH_2CH_3$	
Butyric anhydride	**46** R = R' = $CO(CH_2)_2CH_3$	
Benzoic anhydride	**47** R = H, R' = COC_6H_5	**48** R = R' = COC_6H_5

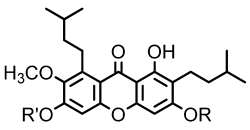
Reagents: (a) H_2, Pd–C, MeOH.

Chart 3. Alkylation and Acylation Reactions of Tetrahydro α-Mangostin (**15**)

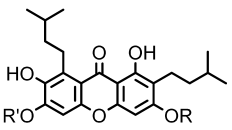
Table 1. MIC Values (μg/mL) of the α-Mangostin Analogs against *M. tuberculosis* $H_{37}Ra$ Strain



1, 6–14



15–18, 24–48



19–22

Compound	MIC	Compound	MIC
1 (R=R′=H)	6.25	**27** (R=H, R′=CH_2CH_2OH)	1.56
6 (R=H, R′=CH_3)	6.25	**28** (R=R′=CH_2CH_2OH)	3.12
7 (R=R′=CH_3)	Inactive[a)]	**29** (R=H, R′=CH_2CONH_2)	1.56
8 (R=H, R′=CH_2CH_3)	6.25	**30** (R=R′=CH_2CONH_2)	Inactive[a)]
9 (R=CH_2CH_3, R′=H)	6.25	**31** (R=H, R′=$CH_2CH=CH_2$)	0.78
10 (R=R′=CH_2CH_3)	Inactive[a)]	**32** (R=R′=$CH_2CH=CH_2$)	Inactive[a)]
11 (R=H, R′=$COCH_3$)	12.5	**33** (R=H, R′=$CH_2CH_2CH_3$)	0.78
12 (R=R′=$COCH_3$)	12.5	**34** (R=H, R′=$(CH_2)_3CH_3$)	1.56
13 (R=H, R′=COC_6H_5)	12.5	**35** (R=R′=$(CH_2)_3CH_3$)	Inactive[a)]
14 (R=R′=COC_6H_5)	Inactive[a)]	**36** (R=H, R′=$(CH_2)_4Br$)	12.5
15 (R=R′=H)	1.56	**37** (R=R′=$(CH_2)_4Br$)	200.0
16 (R=H, R′=CH_3)	0.78	**38** (R=H, R′=$(CH_2)_4CH_3$)	Inactive[a)]
17 (R=R′=CH_3)	Inactive[a)]	**39** (R=H, R′=$CH_2C_6H_5$)	6.25
18 (R=CH_3, R′=H)	12.5	**40** (R=R′=$CH_2C_6H_5$)	12.5
19 (R=R′=H)	6.25	**41** (R=H, R′=$COCH_3$)	6.25
20 (R=CH_3, R′=H)	25.0	**42** (R=$COCH_3$, R′=H)	3.12
21 (R=H, R′=CH_3)	3.12	**43** (R=R′=$COCH_3$)	3.12
22 (R=R′=CH_3)	Inactive[a)]	**44** (R=$COCH_3$, R′=CH_3)	100.0
23	50.0	**45** (R=R′=$COCH_2CH_3$)	1.56
24 (R=H, R′=CH_2CH_3)	1.56	**46** (R=R′=$CO(CH_2)_2CH_3$)	25.0
25 (R=CH_2CH_3, R′=H)	12.5	**47** (R=H, R′=COC_6H_5)	3.12
26 (R=R′=CH_2CH_3)	Inactive[a)]	**48** (R=R′=COC_6H_5)	12.5
Kanamycin	2.5	Isoniazid	0.06
Rifampin	0.004		

a) Inactive at MIC >200 μg/mL.

parent compound **1** (MIC 6.25 μg/mL).[13)] The disubstituted analogs **7**, **10** and **14** were inactive in the same test, except for the 3,6-di-*O*-acetate **12** which remained active at MIC 12.5 μg/mL. The 3-*O*-ethyl ether **9** exhibited the same extent of activity as that of its isomeric 6-*O*-ethyl analog **8** with the same MIC 6.25 μg/mL. These results suggested that no enhancement in activity of the 3- or 6-substituted xanthone with respect to **1**.

We then explored the effect of prenyl group on the xanthone nucleus. The tetrahydro α-mangostin derivative **15** initially prepared displayed increased inhibitory activity (MIC 1.56 μg/mL) with 4-fold more active than the reported natural parent α-mangostin **1**. Tetrahydro γ-mangostin (**19**) (MIC 6.25 μg/mL) which bears isopentyl groups also showed about 8-fold more potency than γ-mangostin (**3**) (MIC 50 μg/mL) with isopentenyl functions.[15] Replacing the 7-OCH_3 in **15** with OH group in **19** (MIC 6.25 μg/mL) caused 4-fold decrease in activity. These results indicated that the isopentyl moiety at C-2 and C-8 together with the methoxyl at C-7 positions of mangostin feature improved the antituberculosis activity. We then focused our attention on exploring the antitubercular activity of the methoxyl functions at various positions on xanthone nucleus.

From Table 1, the 3-monomethyl ether **20** (MIC 25 μg/mL) displayed much lower activity compared with the 7-monomethyl ether in tetrahydro α-mangostin **15** (MIC 1.56 μg/mL) whereas similar antituberculosis effect was observed for the 6-monomethyl ether **21** (MIC 3.12 μg/mL). The 3,7-di-*O*-methyl ether **18** (MIC 12.5 μg/mL) also exhibited 8-fold decrease in activity compared with **15** but the 3,6-dimethyl analog **22** was inactive (MIC >200 μg/mL) under the same screening. The free hydroxyl group at peri carbon C-1 was crucial as was evident from the activity of the 1,7-dimethyl ether derivative **23** (MIC 50 μg/mL) which was 32-fold less potent than that of compound **15**. This evidence led to the conclusion that the methoxyl groups at C-6 or C-7 together with the free 1-OH of tetrahydro α-mangostin structure are important for high antituberculosis activity.

We therefore further focused on exploring variants of the alkyl ethers and ester groups at C-3 and C-6 in **15** and studied their effects on antituberculosis activity. As expected, the 6,7-dimethylated analog **16** which bears an additional methoxyl moiety, as compared with **15**, showed the highest activity at MIC value of 0.78 μg/mL (or 1.82 μM) and was approximately 8-fold more potent than the parent compound **1** and about 2.4-fold more potent than kanamycin (MIC 2.5 μg/mL or 4.29 μM). Potent activity of higher 6-*O*-alkyl ether analog was also observed in compounds **24** (*O*-ethyl), **27** (*O*-hydroxyethyl), **29** (*O*-acetamide), **31** (*O*-allyl), **33** (*O*-propyl) and **34** (*O*-butyl) with MICs 0.78–1.56 μg/mL. As the length of carbon chain increases in **36** (*O*-4-bromobutyl), **38** (6-*O*-pentyl ether) and **39** (*O*-benzyl), the MICs of which were 12.5, >200 and 6.25 μg/mL, respectively, the antimycobacterial properties was decreased. No preference in activity of the 3-*O*-alkyl ether **18** and **25** (MIC 12.5 μg/mL) over their corresponding isomeric 6-*O*-alkylated analogs **16** and **24** (MICs 0.78–1.56 μg/mL) was observed. The essential of the free 3-OH was evidenced from the complete loss or almost loss in activity for the 3,6-di-*O*-methyl ether **17** and other higher alkyl ethers **26** (di-*O*-ethyl), **30** (di-*O*-actamide), **32** (di-*O*-allyl), **35** (di-*O*-butyl) and **37** (di-*O*-4-bromobutyl), which were consistent with that of α-mangostin analog series. A dramatic decrease in activity was also observed in the 3-OAc–6-OMe substitution in **44** (MIC 100 μg/mL). However, the potent activity of di-*O*-(2-hydroxyethyl) **28** (MIC 3.12 μg/mL) and di-*O*-benzyl **40** (MIC 12.5 μg/mL) were unclear at this stage. Interestingly, the 6-mono- (**11**, **13**, **41**, **42**, **47**) and di-*O*-acyl analogs (**12**, **43**, **45**, **46**, **48**) retained moderate to good antimycobacterial activity against *M. tuberculosis* (MICs 3.12–25 μg/mL) when compared with their di-*O*-alkylated series. This could possibly be due to hydrolysis of the ester bonds has taken placed upon uptake into the cells to yield the mono-acyl derivatives or parent compounds **6** or **15**.

The highly active analogs **15**, **16**, **24**, **31** and **33** were then selected for their activity evaluations against the virulent *M. tuberculosis* H_{37}Rv and the multidrug-resistant (MDR) clinical strains. As shown in Table 2, compounds **15**, **16** and **24** remained at the same high levels of activity (MICs 0.78–1.56 μg/mL) against the H_{37}Rv (entry 2) whereas **31** and **33** showed weaker levels with MICs of 1.56–3.12 μg/mL. Among the tested compounds, the 6-*O*-methyl tetrahydro α-mangostin (**16**) was the most active analog and also retained the high activity against the isoniazid (INH)-, rifampin (RMP)-, etambutol (EMB)- and streptomycin (SM)-resistant isolates (entries 4, 7,

Table 2. *In Vitro* Activity of the Tetrahydro α-Mangostin (**15**) and Its 6-*O*-Alkyl Analogs **16**, **24**, **31** and **33** against Multidrug-Resistant *M. tuberculosis* Compared with H_{37}Ra and H_{37}Rv Strains

Entry	Code	Isolate resistant profiles	MIC (μg/mL)				
			15	**16**	**24**	**31**	**33**
1	H_{37}Ra	Pan sensitive	1.56	0.78	1.56	0.78	0.78
2	H_{37}Rv	Pan sensitive	1.56	0.78	1.56	3.12	3.12
3	M3[a]	INH, RMP, SM	1.56	0.78	1.56	3.12	3.12
4	M4[b]	INH, RMP, EMB, SM	1.56	1.56	1.56	3.12	3.12
5	M5[a]	INH, RMP, SM	1.56	1.56	1.56	3.12	3.12
6	M6[c]	INH, RMP	1.56	1.56	1.56	3.12	3.12
7	M8[b]	INH, RMP, EMB, SM	3.12	0.78	3.12	1.56	3.12
8	M11[c]	INH, RMP	1.56	3.12	1.56	3.12	6.25
9	M16[d]	INH, RMP, EMB	3.12	3.12	3.12	3.12	6.25
10	M21[b]	INH, RMP, EMB, SM	3.12	1.56	3.12	3.12	6.25
11	M22[c]	INH, RMP	3.12	1.56	3.12	3.12	6.25
12	M27[c]	INH, RMP	3.12	1.56	1.56	3.12	3.12

INH, isoniazid; RMP, rifampin; EMB, ethambutol; SM, streptomycin. MICs of positive controls against multidrug-resistant *M. tuberculosis* isolates. *a*) INH ≥2 μg/mL, RMP >2 μg/mL, SM ≥8 μg/mL. *b*) INH ≥2 μg/mL, RMP >2 μg/mL, EMB ≥8 μg/mL, SM >8 μg/mL. *c*) INH 2 μg/mL, RMP ≥2 μg/mL. *d*) INH 2 μg/mL, RMP >2 μg/mL, EMB >8 μg/mL.

10) with MIC range of 0.78–1.56 μg/mL. For the INH-, RMP-, and EMB-resistant isolates (entries 3, 5, 9), and the INH- and RMP-strains (entries 6, 8, 11, 12) compound **16** exhibited activities at MICs 0.78–3.12 and 1.56–3.12 μg/mL, respectively. Tetrahydro α-mangostin (**15**) displayed comparable activities as its 6-*O*-ethyl analog **24** at the MIC range of 1.56–3.12 μg/mL whereas the *O*-allyl and *O*-propyl substituted **31** and **33** (MICs 1.56–6.25 μg/mL) were 4 to 8-fold less active than the methyl ether **16**.

Conclusion

A new series of tetrahydro α-mangostin analogs has been synthesized based on mangostin and their antimycobacterial activity was assessed. The present SAR study revealed that the monoalkylated analogs were highly potent inhibitors of *M. tuberculosis* $H_{37}Ra$ and $H_{37}Rv$ and the MDR clinical isolates. The analogs **15**, **16** and **24** exhibited outstanding activity against most MDR *M. tuberculosis*. These compounds should be selected as structure leads for further drug discovery work.

Experimental

Chemistry ^{1}H- and ^{13}C-NMR spectra were carried out using a Bruker AVANCE 300 FT-NMR spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). Electrospray (ES) mass spectra were obtained using a Finnigan Polaris Q and a Finnigan LC-Q mass spectrometer, respectively. High resolution mass spectra were obtained using a Bruker micrOTOF and a Finnigan MAT90 instrument. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum BX spectrophotometer. Melting points were determined on a Griffin melting point apparatus and are uncorrected. Progress of the reactions was monitored using TLC sheet precoated with UV fluorescent Merck silica gel 60 F_{254} and were visualized under UV light and by spraying with anisaldehyde–H_2SO_4 reagent followed by heating. Column chromatography was carried out using Merck silica gel 60 (<0.063 mm).

Isolation and Identification of α-Mangostin (**1**): The crude mangosteen extract obtained from the dried fruit peel as previously described was subjected to quick column chromatography using silica gel as the adsorbent (hexane–acetone, gradient elution) resulted in the isolation of **1** in 3.5% yield based on the dried plant material. The spectroscopic (IR, ^{1}H-NMR and mass spectra) data were consistent with the reported values.[15] All chemicals were obtained from Aldrich, Sigma, Fluka or Merck chemicals.

General Procedure for the Preparation of *O*-Substituted α-Mangostins 6–8, 10–14 and *O*-Substituted Tetrahydro α-Mangostins 16–17, 24, 26–32, 34–41 and 43–48 To a solution of α-mangostin (**1**) (0.37 mmol) or tetrahydro α-mangostin **15** (0.37 mmol) and anhydrous potassium carbonate (0.74 mmol) in anhydrous acetone or *N*,*N*-dimethylformamide (DMF) (1–2 mL) was added different alkyl halides or acyl acid anhydride, or acid halides (0.37 mmol). The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC. Water was then added and the mixture was extracted with ethyl acetate. The combined organic phase was washed with H_2O, dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The reaction mixture was purified by column chromatography using hexane–acetone to yield the corresponding 6-*O*-substituted and 3,6-di-*O*-substituted products.

6-*O*-Methyl α-Mangostin (**6**): Yield 38%; pale yellow amorphous; mp 95–97°C (lit. mp 91–92°C[16]); IR (KBr) cm^{-1}: 3412, 2915, 1649, 1610, 1462, 1382, 1278, 1213 and 1109; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.65 and 1.75 (each s, each 3H, H-15, H-20), 1.82 (s, 6H, H-14, H-19), 3.43 (d, 2H, J=7.1 Hz, H-11), 3.77 (s, 3H, 7-OCH_3), 3.93 (s, 3H, 6-OCH_3), 4.10 (d, 2H, J=6.4 Hz, H-16), 5.23 (m, 2H, H-12, H-17), 6.22 (s, 1H, 3-OH), 6.26 (s, 1H, H-4), 6.72 (s, 1H, H-5) and 13.82 (s, 1H, 1-OH); electrospray ionization (ESI)-MS *m*/*z*: 447 $[M+Na]^+$.

3,6-Di-*O*-methyl α-Mangostin (**7**): Yield 32%; pale yellow amorphous; mp 93–95°C (lit. mp 120–122°C[17]); IR (KBr) cm^{-1}: 3434, 2926, 1646, 1595, 1458, 1429, 1281, 1213, 1173 and 1119; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.67 (s, 6H, H-15, H-20), 1.79 and 1.84 (each s, each 3H, H-14, H-19), 3.34 (d, 2H, J=6.9 Hz, H-11), 3.79 (s, 3H, 7-OCH_3), 3.89 (s, 3H, 3-OCH_3), 3.95 (s, 3H, 6-OCH_3), 4.12 (d, 2H, J=6.3 Hz, H-16), 5.20 (brt, 1H, J=6.9 Hz, H-12), 5.23 (brt, 1H, J=6.3 Hz, H-17), 6.30 (s, 1H, H-4), 6.72 (s, 1H, H-5) and 13.48 (s, 1H, 1-OH); ESI-MS *m*/*z*: 439 $[M+H]^+$.

6-*O*-Ethyl α-Mangostin (**8**): Yield 35%; yellow amorphous; mp 135–136°C; IR (neat) cm^{-1}: 3409, 2922, 1643, 1598, 1464, 1426, 1372, 1279, 1200 and 1111; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.50 (t, 3H, J=6.9 Hz, $OCH_2C\underline{H}_3$), 1.65 and 1.75 (each s, each 3H, H-14, H-19), 1.82 (s, 6H, H-15, H-20), 3.43 (d, 2H, J=7.1 Hz, H-11), 3.78 (s, 3H, OCH_3), 4.10 (d, 2H, J=6.7 Hz, H-16), 4.13 (q, 2H, J=6.9 Hz, $OC\underline{H}_2CH_3$), 5.24 (m, 2H, H-12, H-17), 6.21 (brs, 1H, 3-OH), 6.25 (s, 1H, H-4), 6.68 (s, 1H, H-5) and 13.85 (s, 1H, 1-OH); ESI-MS *m*/*z*: 439 $[M+H]^+$; high resolution (HR)-FAB-MS *m*/*z*: 439.2119 $[M+H]^+$ (Calcd for $C_{26}H_{30}O_6$+H: 439.2120).

3,6-di-*O*-Ethyl α-Mangostin (**10**): Yield 31%; pale yellow amorphous; mp 96–98°C (lit. mp 112–114°C[17]); IR (KBr) cm^{-1}: 3448, 2918, 1642, 1596, 1467, 1433, 1387, 1279, 1204 and 1121; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.47 (brt, 3H, J=7.0 Hz, 3-$OCH_2C\underline{H}_3$), 1.53 (brt, 3H, J=6.9 Hz, 6-$OCH_2C\underline{H}_3$),1.66 and 1.68 (each s, each 3H, H-15, H-20), 1.78 and 1.82 (each s, each 3H, H-14, H-19), 3.36 (d, 2H, J=7.1 Hz, H-11), 3.80 (s, 3H, 7-OCH_3), 4.12 (m, 6H, H-16, 3-$OC\underline{H}_2CH_3$, 6-$OC\underline{H}_2CH_3$), 5.24 (m, 2H, H-12, H-17), 6.27 (s, 1H, H-4), 6.69 (s, 1H, H-5) and 13.49 (s, 1H, 1-OH); ESI-MS *m*/*z*: 489 $[M+Na]^+$.

α-Mangostin 6-*O*-Acetate (**11**): Yield 10%; pale yellow amorphous; mp 137–138°C; IR (KBr) cm^{-1}: 3413, 3313, 2913, 1756, 1735, 1645, 1616, 1598, 1463, 1424, 1374, 1315, 1277, 1243, 1187, 1148, 1080, 1045 and 817; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.66 and 1.73 (each s, each 3H, H-14, H-15), 1.81 (s, 6H, H-19, H-20), 2.37 (s, 3H, $COCH_3$), 3.44 (d, 2H, J=7.0 Hz, H-11), 3.74 (s, 3H, OCH_3), 4.10 (d, 2H, J=6.2 Hz, H-16), 5.18 (brt, 1H, J=6.2 Hz, H-17), 5.24 (brt, 1H, J=7.0 Hz, H-12), 6.27 (s, 2H, H-4, 3-OH), 7.07 (s, 1H, H-5) and 13.57 (s, 1H, 1-OH); ESI-MS *m*/*z*: 451 $[M-H]^-$; HR-time-of-flight (TOF)-MS *m*/*z*: 451.1833 $[M-H]^-$; Calcd for $C_{26}H_{28}O_7-H$, 451.1801.

α-Mangostin 3,6-Di-*O*-acetate (**12**): Yield 17%; yellow amorphous; mp 110–112°C; (lit. mp 113–114°C[17]); IR (KBr) cm^{-1}: 3477, 2922, 1779, 1602, 1462, 1429, 1372, 1274 and 1184; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.60 (s, 6H, H-15, H-20), 1.75 and 1.81 (each s, each 3H, H-14, H-19), 2.32 (s, 3H, $COC\underline{H}_3$), 2.37 (s, 3H, $COC\underline{H}_3$), 3.29 (d, 2H, J=5.8 Hz, H-11), 3.75 (s, 3H, OCH_3), 4.12 (d, 2H, J=5.8 Hz, H-16), 5.16 (brt, 2H, J= 5.8 Hz, H-12, H-17), 6.61 (s, 1H, H-4), 7.10 (s, 1H, H-5) and 13.40 (s, 1H, 1-OH); ESI-MS *m*/*z*: 495 $[M+H]^+$.

α-Mangostin 6-*O*-Benzoate (**13**): Yield 6%; yellow amorphous; mp 188–189°C; IR (KBr) cm^{-1}: 3423, 2923, 1752, 1645, 1607, 1462, 1382, 1260, 1183, 1148, 1087, 820 and 706; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 1.69 and 1.83 (each s, each 3H, H-19, H-20), 1.76 and 1.83 (each s, each 3H, H-14, H-15), 3.44 (d, 2H, *J*=7.0 Hz, H-11), 3.76 (s, 3H, OCH_3), 4.16 (d, 2H, *J*=6.0 Hz, H-16), 5.26 (brt, 2H, *J*=5.4 Hz, H-12, H-17), 6.24 (s, 1H, H-4), 6.43 (s, 1H, 3-OH), 7.22 (s, 1H, H-5), 7.56 (brt, 1H, *J*=7.5 Hz, Ar-H), 7.69 (brt, 2H, *J*=7.3 Hz, Ar-H), 8.25 (d, 2H, *J*=7.4 Hz, Ar-H) and 13.55 (s, 1H, 1-OH); HR-FAB-MS *m/z*: 515.2058 $[M+H]^+$ (Calcd for $C_{31}H_{30}O_7$+H: 515.2070).

α-Mangostin 3,6-Di-*O*-benzoate (**14**): Yield 10%; Pale yellow amorphous; mp 85–86°C; IR (KBr) cm^{-1}: 3420, 2918, 1743, 1602, 1455, 1426, 1253, 1177 and 1144; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 1.71 and 1.84 (each s, each 3H, H-14, H-15, H-19, H-20), 3.39 (d, 2H, *J*=6.7 Hz, H-11), 4.19 (d, 2H, *J*=6.0 Hz, H-16), 3.79 (s, 3H, 3-OCH_3), 5.22 and 5.24 (each brt, each 1H, *J*=6.0, 6.7 Hz, H-12, H-17), 6.78 (s, 1H, H-4), 7.29 (s, 1H, H-5), 7.54–8.23 (m, 10H, Ar-H) and 13.49 (s, 1H, 1-OH); HR-FAB-MS *m/z*: 619.2322 $[M+H]^+$ (Calcd for $C_{38}H_{34}O_8$+H: 619.2341).

6-*O*-Methyltetrahydro *α*-Mangostin (**16**): Yield 31%; pale yellow amorphous; mp 115–116°C; IR (KBr) cm^{-1}: 3476, 3200, 2953, 1613, 1470, 1368, 1266, 1193, 1121, 1067, 1034, 980 and 819; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.9 Hz, H-14, H-15), 0.97 (d, 6H, *J*=7.0 Hz, H-19, H-20), 1.40 (brq, 2H, *J*=7.6 Hz, H-12), 1.46 (brq, 2H, *J*=7.6 Hz, H-17), 1.62 (m, 1H, H-13), 1.74 (m, 1H, H-18), 2.63 (brt, 2H, *J*=7.6 Hz, H-11), 3.32 (brt, 2H, *J*=7.6 Hz, H-16), 3.80 (s, 3H, 7-OCH_3), 3.93 (s, 3H, 6-OCH_3), 5.69 (brs, 1H, 3-OH), 6.22 (s, 1H, H-4), 6.68 (s, 1H, H-5) and 13.87 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 427.2124 $[M-H]^-$ (Calcd for $C_{25}H_{32}O_6$−H: 427.2126).

3,6-Di-*O*-methyltetrahydro *α*-Mangostin (**17**): Yield 35%; pale yellow solid; mp 92–94°C; IR (KBr) cm^{-1}: 3416, 2915, 1599, 1462, 1375, 1278, 1209 and 1141; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.5 Hz, H-19, H-20), 1.38 (brq, 2H, *J*=7.7 Hz, H-12), 1.40 (brq, 2H, *J*=7.9 Hz, H-17), 1.58 (m, 1H, H-13), 1.73 (m, 1H, H-18), 2.62 (brt, 2H, *J*=7.7 Hz, H-11), 3.33 (brt, 2H, *J*=7.9 Hz, H-16), 3.80 (s, 3H, 7-OCH_3), 3.86 (s, 3H, 3-OCH_3), 3.94 (s, 3H, 6-OCH_3), 6.28 (s, 1H, H-4), 6.69 (s, 1H, H-5) and 13.62 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 443.2429 $[M+H]^+$ (Calcd for $C_{26}H_{34}O_6$+H: 443.2428).

6-*O*-Ethyltetrahydro *α*-Mangostin (**24**): Yield 38%; pale yellow amorphous; mp 129–130°C; IR (KBr) cm^{-1}: 3303, 2956, 2870, 1634, 1605, 1587, 1456, 1399, 1286, 1195, 1129, 1070, 928 and 820; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.7 Hz, H-19, H-20), 1.41 (m, 4H, H-12, H-17), 1.54 (t, 3H, *J*=6.9 Hz, $OCH_2C\underline{H}_3$), 1.62 (m, 1H, H-13), 1.74 (m, 1H, H-18), 2.63 (dt, 2H, *J*=5.7, 8.0 Hz, H-11), 3.32 (dt, 2H, *J*=5.2, 7.8 Hz, H-16), 3.81 (s, 3H, 7-OCH_3), 4.14 (q, 2H, *J*=6.9 Hz, $OC\underline{H}_2CH_3$), 5.41 (brs, 1H, 3-OH), 6.22 (s, 1H, H-4), 6.67 (s, 1H, H-5) and 13.88 (s, 1H, 1-OH); HR-FAB-MS *m/z*: 443.2439 $[M+H]^+$ (Calcd for $C_{26}H_{34}O_6$+H: 443.2433).

3,6-Di-*O*-ethyltetrahydro *α*-Mangostin (**26**): Yield 42%; pale yellow amorphous; mp 75–76°C; IR (KBr) cm^{-1}: 2948, 2865, 1638, 1600, 1466, 1384, 1364, 1285, 1202, 1140, 854 and 813; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.5 Hz, H-19, H-20), 1.38-1.41 (m, 4H, H-12, H-17), 1.43 (t, 3H, *J*=6.8 Hz, 3-$OCH_2C\underline{H}_3$), 1.51 (t, 3H, *J*=6.9 Hz, 6-$OCH_2C\underline{H}_3$), 1.60 (m, 1H, H-13), 1.73 (m, 1H, H-18), 2.61 (brt, 2H, *J*=7.7 Hz, H-11), 3.31 (brt, 2H, *J*=7.9 Hz, H-16), 3.81 (s, 3H, 7-OCH_3), 4.04 (q, 2H, *J*=6.8 Hz, 3-$OC\underline{H}_2CH_3$), 4.12 (q, 2H, *J*=6.9 Hz, 6-$OC\underline{H}_2CH_3$), 6.21 (s, 1H, H-4), 6.63 (s, 1H, H-5) and 13.63 (s, 1H, 1-OH); HR-FAB *m/z*: 471.2746 $[M+H]^+$ (Calcd for $C_{28}H_{38}O_6$+H: 471.2746).

6-*O*-(2-Hydroxyethyl)tetrahydro *α*-Mangostin (**27**): Yield 38%; pale yellow amorphous; mp 79–80°C; IR (KBr) cm^{-1}: 3279, 3143, 2953, 1703, 1642, 1586, 1464, 1366, 1272, 1197, 1128, 1038 and 823; ^{1}H-NMR ($CDCl_3$+CD_3OD, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.40 (m, 2H, H-12), 1.42 (m, 2H, H-17), 1.61 (m, 1H, H-13), 1.76 (m, 1H, H-18), 2.61 (dt, 2H, *J*=5.6, 7.9 Hz, H-11), 3.31 (dt, 2H, *J*=5.4, 8.0 Hz, H-16), 3.82 (s, 3H, 7-OCH_3), 4.05 (t, 2H, *J*=4.4 Hz, $OCH_2C\underline{H}_2OH$), 4.16 (t, 2H, *J*=4.4 Hz, $OC\underline{H}_2CH_2OH$), 5.04 (brs, 1H, 3-OH), 6.18 (s, 1H, H-4), 6.63 (s, 1H, H-5) and 13.78 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 457.2221 $[M-H]^-$ (Calcd for $C_{26}H_{34}O_7$−H: 457.2232).

3,6-Di-*O*-(2-hydroxyethyl)tetrahydro *α*-Mangostin (**28**): Yield 30%; pale yellow amorphous; mp 110–112°C; IR (KBr) cm^{-1}: 3503, 2954, 2869, 1761, 1624, 1602, 1461, 1425, 1286, 1238, 1177, 1125, 1038 and 842; ^{1}H-NMR ($CDCl_3$+CD_3OD, 300 MHz) *δ*: 0.91 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.86 (d, 6H, *J*=6.5 Hz, H-19, H-20), 1.24 (brq, 2H, *J*=8.0 Hz, H-12), 1.29 (brq, 2H, *J*=10.8 Hz, H-17), 1.46 (m, 1H, H-13), 1.62 (m, 1H, H-18), 2.53 (brt, 2H, *J*=8.0 Hz, H-11), 3.22 (brt, 2H, *J*=10.8 Hz, H-16), 3.71 (s, 3H, 7-OCH_3), 3.87 (brs, 4H, 3-, 6-$OCH_2C\underline{H}_2OH$), 4.01 (t, 2H, *J*=4.9 Hz, 3-$OC\underline{H}_2CH_2OH$), 4.05 (t, 2H, *J*=4.9 Hz, 6-$OC\underline{H}_2CH_2OH$), 6.21 (s, 1H, H-4), 6.62 (s, 1H, H-5) and 13.62 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 501.2491 $[M-H]^-$ (Calcd for $C_{28}H_{38}O_8$−H: 501.2494).

Tetrahydro *α*-Mangostin-6-*O*-acetamide (**29**): Yield 55%; pale yellow amorphous; mp 208–210°C; IR (KBr) cm^{-1}: 3441, 3180, 2955, 2868, 1652, 1610, 1587, 1466, 1423, 1295, 1273, 1195, 1132, 1071, 1036, 999 and 834; ^{1}H-NMR ($CDCl_3$+CD_3OD, 300 MHz) *δ*: 0.88 (d, 6H, *J*=6.4 Hz, H-14, H-15), 0.92 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.35 (m, 4H, H-12, H-17), 1.55 (m, 1H, H-13), 1.68 (m, 1H, H-18), 2.57 (brt, 2H, *J*=8.2 Hz, H-11), 3.27 (brt, 2H, *J*=8.1 Hz, H-16), 3.77 (s, 3H, OCH_3), 4.52 (s, 2H, OCH_2CONH_2), 6.19 (s, 1H, H-4), 6.63 (s, 1H, H-5); HR-TOF-MS *m/z*: 454.2209 $[M-H]^-$ (Calcd for $C_{26}H_{33}NO_6$−H: 454.2206).

Tetrahydro *α*-Mangostin-3,6-di-*O*-acetamide (**30**): Yield 47%; pale yellow amorphous; mp 230°C; IR (KBr) cm^{-1}: 3441, 3180, 2955, 2868, 1653, 1610, 1587, 1466, 1423, 1295, 1273, 1195, 1132, 1071, 1036, 999 and 834; ^{1}H-NMR (DMSO-d_6, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.3 Hz, H-14, H-15), 0.95 (d, 6H, *J*=6.3 Hz, H-19, H-20), 1.35 (m, 4H, H-12, H-17), 1.53 (m, 1H, H-13), 1.68 (m, 1H, H-18), 2.60 (m, 2H, H-11), 3.27 (m, 2H, H-16), 3.79 (s, 3H, OCH_3), 4.60 and 4.70 (each s, each 2H, 3-, 6-$OC\underline{H}_2CONH_2$), 6.45 (s, 1H, H-4), 6.91 (s, 1H, H-5), 7.49 (m, 4H, $CONH_2$), 13.55 (s, 1H, 1-OH); ESI-MS: *m/z* 511 $[M-H]^-$, HR-TOF-MS *m/z*: 511.2410 $[M-H]^-$ (Calcd for $C_{28}H_{36}N_2O_7$−H: 511.2407).

6-*O*-Allyltetrahydro *α*-Mangostin (**31**): Yield 59%; pale yellow amorphous; mp 59–60°C; IR (KBr) cm^{-1}: 3433, 2956, 1642, 1605, 1463, 1424, 1287, 1198, 1126, 1038, 991 and 822; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.41 (m, 4H, H-12, H-17), 1.57 (m, 1H, H-13), 1.74 (m, 1H, H-18), 2.63 (brt, 2H, *J*=7.8 Hz, H-11), 3.31 (brt, 2H, *J*=7.8 Hz, H-16), 3.82 (s, 3H, 7-OCH_3), 4.65 (d, 2H, *J*=4.2 Hz, $OC\underline{H}_2$–CH=CH_2), 5.42 (dd,

2H, *J*=10.7, 16.8 Hz, OCH_2–CH=C$\underline{H_2}$), 5.45 (s, 1H, 3-OH), 6.06 (m, 1H, OCH_2–C$\underline{H}$=CH_2), 6.22 (s, 1H, H-4), 6.68 (s, 1H, H-5) and 13.87 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 453.2273 $[M-H]^-$ (Calcd for $C_{27}H_{34}O_6$−H: 453.2283).

3,6-Di-*O*-allyltetrahydro *α*-Mangostin (**32**): Yield 24%; pale yellow amorphous; mp 78–79°C; IR (KBr) cm^{-1}: 2954, 2869, 1638, 1596, 1466, 1432, 1381, 1286, 1195, 1134, 1096, 976, 859 and 817; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.38 (brq, 2H, *J*=7.8 Hz, H-12), 1.40 (brq, 2H, *J*=8.0 Hz, H-17), 1.59 (m, 1H, H-13), 1.72 (m, 1H, H-18), 2.66 (dt, 2H, *J*=5.5, 7.8 Hz, H-11), 3.33 (dt, 2H, *J*=5.7, 8.0 Hz, H-16), 3.82 (s, 3H, 7-OCH_3), 4.58 (dd, 2H, *J*=1.4, 4.8 Hz, 3-OC$\underline{H_2}$–CH=CH_2), 4.65 (dd, 2H, *J*=1.3, 5.0 Hz, 6-OC$\underline{H_2}$–CH=CH_2), 5.30 (dd, 1H, *J*=1.4, 10.5 Hz, 3-OCH_2–CH=C$\underline{H_2}$), 5.34 (dd, 1H, *J*=1.3, 9.2 Hz, 6-OCH_2–CH=C$\underline{H_2}$), 5.43 (dd, 1H, *J*=1.4, 14.8 Hz, 3-OCH_2–CH=C$\underline{H_2}$), 5.49 (dd, 1H, *J*=1.3, 10.0 Hz, 6-OCH_2–CH=C$\underline{H_2}$), 6.05 (m, 2H, 3-, 6-OCH_2–C$\underline{H}$=CH_2), 6.26 (s, 1H, H-4), 6.68 (s, 1H, H-5) and 13.63 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 495.2750 $[M+H]^+$ (Calcd for $C_{30}H_{38}O_6$+H: 495.2741).

6-*O*-Butyltetrahydro *α*-Mangostin (**34**): Yield 31%; yellow amorphous; mp 79–80°C; IR (KBr) cm^{-1}: 3446, 2956, 1636, 1604, 1464, 1286, 1196, 1124, 1038 and 822; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.7 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.7 Hz, H-19, H-20), 0.99 (t, 3H, *J*=8.2 Hz, $OCH_2CH_2CH_2C\underline{H_3}$), 1.40 (m, 2H, H-12), 1.43 (m, 2H, H-17), 1.55 (m, 2H, $OCH_2CH_2C\underline{H_2}CH_3$), 1.61 (m, 1H, H-13), 1.76 (m, 1H, H-18), 1.93 (quint, 2H, *J*=6.4 Hz, $OCH_2C\underline{H_2}CH_2CH_3$), 2.63 (dt, 2H, *J*=5.6, 8.0 Hz, H-11), 3.32 (dt, 2H, *J*=5.3, 8.1 Hz, H-16), 3.81 (s, 3H, 7-OCH_3), 4.06 (t, 2H, *J*=6.4 Hz, $OC\underline{H_2}CH_2CH_2CH_3$), 6.22 (s, 1H, H-4), 6.67 (s, 1H, H-5) and 13.89 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 471.2752 $[M+H]^+$ (Calcd for $C_{26}H_{38}O_6$+H: 471.2741).

3,6-Di-*O*-butyltetrahydro *α*-Mangostin (**35**): Yield 41%; pale yellow viscous; IR (neat) cm^{-1}: 3445, 2956, 2870, 1646, 1598, 1462, 1285, 1198, 1139, 1101, 823 and 790; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.97 (m, 3H, 3-$OCH_2(CH_2)_2CH_3$), 0.98 (d, 6H, *J*=6.5 Hz, H-19, H-20), 1.00 (m, 3H, 6-$OCH_2CH_2CH_2C\underline{H_3}$), 1.37 (brq, 2H, *J*=8.1 Hz, H-12), 1.42 (brq, 2H, *J*=8.1 Hz, H-17), 1.54 (m, 4H, 3-, 6-$OCH_2CH_2C\underline{H_2}CH_3$), 1.56 (m, 1H, H-13), 1.71 (m, 1H, H-18), 1.79 (quint, 2H, *J*=6.1 Hz, 3-$OCH_2C\underline{H_2}CH_2CH_3$), 1.85 (quint, 2H, *J*=6.4 Hz, 6-$OCH_2C\underline{H_2}CH_2CH_3$), 2.63 (brt, 2H, *J*=8.1 Hz, H-11), 3.32 (brt, 2H, *J*=8.1 Hz, H-16), 3.80 (s, 3H, 7-OCH_3), 4.01 (brt, 2H, *J*=6.1 Hz, 3-$OC\underline{H_2}CH_2CH_2CH_3$), 4.05 (brt, 2H, *J*=6.4 Hz, 6-$OC\underline{H_2}CH_2CH_2CH_3$), 6.25 (s, 1H, H-4), 6.67 (s, 1H, H-5) and 13.65 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 527.3383 $[M+H]^+$ (Calcd for $C_{32}H_{46}O_6$+H: 527.3367).

6-*O*-(4-Bromobutyl)tetrahydro *α*-Mangostin (**36**): Yield 36%; yellow viscous; IR (neat) cm^{-1}: 3392, 2949, 1638, 1604, 1588, 1460, 1287, 1197 and 1125; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.6 Hz, H-14, H-15), 0.97 (d, 6H, *J*=7.0 Hz, H-19, H-20), 1.21 (brq, 4H, *J*=7.8 Hz, H-12, H-17), 1.60 (m, 1H, H-13), 1.73 (m, 1H, H-18), 2.08 (m, 4H, $OCH_2C\underline{H_2}C\underline{H_2}CH_2Br$), 2.62 (brt, 2H, *J*=7.7 Hz, H-11), 3.32 (t, 2H, *J*=7.7 Hz, H-16), 3.51 (brt, 2H, *J*=5.9 Hz, $OCH_2CH_2CH_2C\underline{H_2}Br$), 3.80 (s, 3H, 7-$OCH_3$), 4.10 (brs, 2H, $OC\underline{H_2}CH_2CH_2CH_2Br$), 5.46 (brs, 1H, 3-OH), 6.22 (s, 1H, H-4), 6.67 (s, 1H, H-5) and 13.86 (s, 1H, 1-OH); HR-TOF-MS: *m/z* 549.1847 $[M+H]^+$; Calcd for $C_{28}H_{37}BrO_6$+H, 549.1846.

3,6-Di-*O*-(4-bromobutyl)tetrahydro *α*-Mangostin (**37**): Yield 21%; yellow amorphous; mp 78–79°C; IR (KBr) cm^{-1}: 3503, 2954, 2869, 1761, 1624, 1602, 1461, 1425, 1286, 1238, 1177, 1125, 1038 and 842; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.36 (brq, 2H, *J*=7.4 Hz, H-12), 1.41 (brq, 2H, *J*=8.2 Hz, H-17), 1.60 (m, 1H, H-13), 1.74 (m, 1H, H-18), 2.01–2.09 (m, 8H, 3-, 6-$OCH_2C\underline{H_2}C\underline{H_2}CH_2Br$), 2.62 (brt, 2H, *J*=7.5 Hz, H-11), 3.32 (brt, 2H, *J*=6.5 Hz, H-16), 3.49 (t, 3H, *J*=6.4 Hz, 3-$OCH_2CH_2CH_2C\underline{H_2}Br$), 3.51 (t, 3H, *J*=5.8 Hz, 6-$OCH_2CH_2CH_2C\underline{H_2}Br$), 3.80 (s, 3H, 7-$OCH_3$), 4.08 (t, 2H, *J*=5.8 Hz, 3-$OC\underline{H_2}CH_2CH_2CH_2Br$), 4.10 (t, 2H, *J*=5.7 Hz, 6-$OC\underline{H_2}CH_2CH_2CH_2Br$) 6.25 (s, 1H, H-4), 6.67 (s, 1H, H-5) and 13.62 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 683.1587 $[M-H]^-$ (Calcd for $C_{32}H_{44}Br_2O_6$−H: 683.1577).

6-*O*-Pentyltetrahydro *α*-Mangostin (**38**): Yield 21%; yellow solid; mp 169–171°C; IR (KBr) cm^{-1}: 3324, 2955, 2863, 1648, 1605, 1587, 1458, 1284, 1198, 1124, 1038 and 823; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.89 (t, 3H, *J*=7.1 Hz, $OCH_2CH_2CH_2CH_2C\underline{H_3}$), 0.95 (d, 6H, *J*=6.8 Hz, H-14, H-15), 0.97 (d, 6H, *J*=7.0 Hz, H-19, H-20), 1.35 (m, 2H, $OCH_2CH_2CH_2C\underline{H_2}CH_3$), 1.42 (m, 2H, H-12), 1.43 (m, 2H, H-17), 1.50 (m, 2H, $OCH_2CH_2C\underline{H_2}CH_2CH_3$), 1.62 (m, 1H, H-13), 1.74 (m, 1H, H-18), 1.87 (quint, 2H, *J*=6.5 Hz, $OCH_2C\underline{H_2}CH_2CH_2CH_3$), 2.63 (brt, 2H, *J*=7.9 Hz, H-11), 3.32 (brt, 2H, *J*=8.0 Hz, H-16), 3.81 (s, 3H, 7-OCH_3), 4.05 (brt, 2H, *J*=6.5 Hz, $OC\underline{H_2}CH_2CH_2CH_2CH_3$), 5.61 (s, 1H, 3-OH), 6.21 (s, 1H, H-4), 6.67 (s, 1H, H-5) and 13.88 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 485.2902 $[M+H]^+$ (Calcd for $C_{29}H_{40}O_6$+H: 485.2897).

6-*O*-Benzyltetrahydro *α*-Mangostin (**39**): Yield 42%; yellow amorphous; mp 109–110°C; IR (KBr) cm^{-1}: 3385, 2953, 2866, 1644, 1608, 1583, 1465, 1382, 1365, 1289, 1194, 1122, 1041 and 819; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.40 (brq, 2H, *J*=7.9 Hz, H-12), 1.44 (brq, 2H, *J*=8.0 Hz, H-17), 1.59 (m, 1H, H-13), 1.74 (m, 1H, H-18), 2.63 (dt, 2H, *J*=5.6, 7.9 Hz, H-11), 3.34 (dt, 2H, *J*=5.3, 8.0 Hz, H-16), 3.83 (s, 3H, 7-OCH_3), 5.17 (s, 2H, $OC\underline{H_2}C_6H_5$), 6.21 (s, 1H, H-4), 6.74 (s, 1H, H-5), 7.38 (m, 5H, $OCH_2C_6\underline{H_5}$) and 13.85 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 505.2590 $[M+H]^+$ (Calcd for $C_{31}H_{36}O_6$+H: 505.2585).

3,6-Di-*O*-benzyltetrahydro *α*-Mangostin (**40**): Yield 25%; yellow amorphous; mp 135–136°C; IR (KBr) cm^{-1}: 2952, 1642, 1600, 1463, 1381, 1285, 1191, 1143, 1040, 825, 785, 731 and 694; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.91 (d, 6H, *J*=6.6 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.9 Hz, H-19, H-20), 1.41 (brq, 2H, *J*=7.8 Hz, H-12), 1.46 (brq, 2H, *J*=8.0 Hz, H-17), 1.62 (m, 1H, H-13), 1.75 (m, 1H, H-18), 2.69 (dt, 2H, *J*=5.6, 7.8 Hz, H-11), 3.34 (dt, 2H, *J*=5.3, 8.0 Hz, H-16), 3.80 (s, 3H, 7-OCH_3), 5.13 (s, 2H, 3-$OC\underline{H_2}C_6H_5$), 5.18 (s, 2H, 6-$OC\underline{H_2}C_6H_5$), 6.33 (s, 1H, H-4), 6.74 (s, 1H, H-5), 7.40 (m, 10H, 3-, 6-$OCH_2C_6\underline{H_5}$) and 13.64 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 595.3038 $[M+H]^+$ (Calcd for $C_{38}H_{42}O_6$+H: 595.3054).

Tetrahydro *α*-Mangostin-6-*O*-acetate (**41**): Yield 10%; pale yellow solid; mp 111–113°C; IR (KBr) cm^{-1}: 3456, 2957, 1781, 1646, 1617, 1606, 1595, 1458, 1426, 1370, 1313, 1288, 1232, 1184, 1154, 1128, 1069, 1024, 982 and 820; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.94 (d, 6H, *J*=6.6 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.40 (brq, 2H, *J*=8.0 Hz, H-12), 1.40 (m, 2H, H-17, H-12), 1.63 (m, 1H, H-13), 1.74 (m, 1H, H-18), 2.39 (s, 3H, $COCH_3$), 2.60 (dt, 2H, *J*=5.6, 8.0 Hz, H-11), 3.32 (dt, 2H, *J*=5.6, 8.0 Hz, H-16), 3.79 (s, 3H, 7-OCH_3), 5.88

(brs, 3-OH), 6.12 (s, 1H, H-4), 7.02 (s, 1H, H-5) and 13.53 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 457.2224 $[M+H]^+$ (Calcd for $C_{26}H_{32}O_7$+H: 457.2220)

Tetrahydro *α*-Mangostin-3,6-di-*O*-acetate (**43**): Yield 67%; yellow amorphous; mp 118–120°C; IR (KBr) cm^{-1}: 2954, 1757, 1635, 1602, 1458, 1433, 1375, 1285, 1195 and 1184; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.6 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.40 (brq, 2H, *J*=8.0 Hz, H-12), 1.43 (brq, 2H, *J*=8.2 Hz, H-17), 1.59 (m, 1H, H-13), 1.75 (m, 1H, H-18), 2.33 and 2.37 (each s, each 3H, 3-, 6-$COCH_3$, respectively), 2.56 (dt, 2H, *J*=5.5, 8.0 Hz, H-11), 3.33 (dt, 2H, *J*=5.1, 8.2 Hz, H-16), 3.80 (s, 3H, 7-OCH_3), 6.59 (s, 1H, H-4), 7.08 (s, 1H, H-5) and 13.53 (s, 1H, 1-OH); HR-FAB-MS *m/z*: 499.2335 $[M+H]^+$ (Calcd for $C_{28}H_{34}O_8$+H: 499.2331).

6-*O*-Methytetrahydro *α*-Mangostin-3-*O*-acetate (**44**): Compound **44** was prepared in a similar manner as for compound **41**, but using **16** in place of trahydro *α*-mangostin: Yield 72%; yellow amorphous; mp 96–98°C; IR (KBr) cm^{-1}: 2955, 2868, 1761, 1638, 1625, 1603, 1461, 1427, 1310, 1282, 1266, 1177, 1150, 1122, 1078 and 840; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.6 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.3 Hz, H-19, H-20), 1.39 (m, 4H, H-12, H-17), 1.55 (m, 1H, H-13), 1.73 (m, 1H, H-18), 2.34 (s, 3H, $COCH_3$), 2.55 (brt, 2H, *J*=8.4 Hz, H-11), 3.32 (brt, 2H, *J*=7.8 Hz, H-16), 3.80 (s, 3H, 7-OCH_3), 3.95 (s, 3H, 6-OCH_3), 6.56 (s, 1H, H-4), 6.71 (s, 1H, H-5) and 13.80 (s, 1H, 1-OH); HR-FAB-MS *m/z*: 469.2237 $[M-H]^-$ (Calcd for $C_{27}H_{34}O_7$−H: 469.2232).

Tetrahydro *α*-Mangostin-3,6-di-*O*-propionate (**45**): Yield 52%; pale yellow amorphous; mp 82–83°C; IR (KBr) cm^{-1}: 3448, 2955, 2868, 1761, 1638, 1625, 1603, 1461, 1427, 1310, 1282, 1266, 1177, 1150, 1122, 1078, 887 and 840; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.95 (d, 6H, *J*=6.6 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.3 Hz, H-19, H-20), 1.29 and 1.30 (each t, each 3H, each *J*=7.5 Hz, 3-, 6-$COCH_2C\underline{H}_3$, respectively), 1.39 (m, 2H, H-12), 1.42 (m, 2H, H-17), 1.59 (m, 1H, H-13), 1.75 (m, 1H, H-18), 2.55 (brt, 2H, *J*=8.4 Hz, H-11), 2.65 (m, 4H, 3-, 6-$COC\underline{H}_2CH_3$), 3.34 (brt, 2H, *J*=7.8 Hz, H-16), 3.78 (s, 3H, 7-OCH_3), 6.59 (s, 1H, H-4), 7.07 (s, 1H, H-5) and 13.54 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 527.2639 $[M+H]^+$ (Calcd for $C_{30}H_{38}O_8$+H: 527.2644).

Tetrahydro *α*-Mangostin-3,6-di-*O*-butyrate (**46**): Yield 57%; pale yellow amorphous; mp 142–144°C; IR (KBr) cm^{-1}: 3383, 2955, 2869, 1735, 1644, 1611, 1464, 1425, 1287, 1208, 1168, 1125, 1125, 1094, 1072, 1036 and 827; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.4 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.5 Hz, H-19, H-20),1.05 (t, 3H, *J*=6.9 Hz, 3-$COCH_2CH_2C\underline{H}_3$), 1.06 (t, 3H, *J*=7.1 Hz, 6-$COCH_2CH_2C\underline{H}_3$), 1.38 (m, 2H, H-12), 1.40 (m, 2H, H-17), 1.55 (m, 1H, H-13), 1.79 (m, 1H, H-18), 1.81 (m, 4H, 3-, 6-$COCH_2C\underline{H}_2CH_3$), 2.55 (brt, 4H, *J*=7.7 Hz, H-11), 2.57 (m, 4H, 3-, 6-$COC\underline{H}_2CH_2CH_3$), 3.33 (brt, 2H, *J*=7.8 Hz, H-16), 3.78 (s, 3H, 7-OCH_3), 6.58 (s, 1H, H-4), 7.06 (s, 1H, H-5) and 13.55 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 555.2962 $[M+H]^+$ (Calcd for $C_{32}H_{43}O_8$+H: 555.2952).

Tetrahydro *α*-Mangostin-6-*O*-benzoate (**47**): Yield 47%; yellow amorphous; mp 171–172°C; IR (KBr) cm^{-1}: 3348, 2952, 2868, 1726, 1609, 1576, 1468, 1432, 1313, 1281, 1258, 1167, 1125, 1093, 848 and 703; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.96 (d, 6H, *J*=6.9 Hz, H-14, H-15), 0.99 (d, 6H, *J*=7.0 Hz, H-19, H-20), 1.42 (m, 4H, H-12, H-17), 1.58 (m, 1H, H-13), 1.76 (m, 1H, H-18), 2.62 (brt, 2H, *J*=7.6 Hz, H-11), 3.36 (brt, 2H, *J*=7.6 Hz, H-16), 3.79 (s, 3H, 7-OCH_3), 5.89 (brs, 1H, 3-OH), 6.16 (s, 1H, H-4), 7.17 (s, 1H, H-5), 7.55 (t, 2H, *J*=7.4 Hz, Ar-H), 7.69 (t, 1H, *J*=7.4 Hz, Ar-H), 8.24 (d, 2H, *J*=7.4 Hz, Ar-H) and 13.57 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 519.2382 $[M+H]^+$ (Calcd for $C_{31}H_{34}O_7$+H: 519.2377).

Tetrahydro *α*-Mangostin-3,6-di-*O*-benzoate (**48**): Yield 3%; yellow amorphous; mp 58–60°C; IR (KBr) cm^{-1}: 2955, 2863, 1747, 1638, 1620, 1601, 1457, 1428, 1244, 1175, 1148, 1119, 1057, 826 and 704; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.86 (d, 6H, *J*=6.4 Hz, H-14, H-15), 1.00 (d, 6H, *J*=6.5 Hz, H-19, H-20), 1.43 (m, 4H, H-12, H-17), 1.57 (m, 1H, H-13), 1.78 (m, 1H, H-18), 2.64 (brt, 2H, *J*=8.0 Hz, H-11), 3.39 (brt, 2H, *J*=8.3 Hz, H-16), 3.81 (s, 3H, 7-OCH_3), 6.76 (s, 1H, H-4), 7.24 (s, 1H, H-5), 7.53 (t, 4H, *J*=7.4 Hz, Ar-H), 7.66 (brt, 1H, *J*=7.4 Hz, Ar-H), 7.67 (brt, 1H, *J*=7.4 Hz, Ar-H), 8.22 (brt, 4H, *J*=7.4 Hz, Ar-H) and 13.61 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 623.2622 $[M+H]^+$ (Calcd for $C_{38}H_{38}O_8$+H: 623.2639).

Preparation of Compounds 9, 25 and 42 To a mixture of *α*-mangostin **1** (102 mg, 0.25 mmol) and anhydrous potassium carbonate (75 mg, 0.25 mmol) in DMF (15 mL) was added diethyl sulfate (120 mg, 0.77 mmol) and the reaction mixture was stirred at room temperature for 5 min. Solvent was then removed under reduced pressure. Water was added and the mixture was extracted with EtOAc. The combined organic phase was washed with H_2O, dried over anhydrous Na_2SO_4 and the solvent removed under vacuum. The reaction mixture was purified by column chromatography using hexane–acetone to yield **9** (12 mg, 10%) together with **10** (36 mg, 31%) and **8** (35 mg, 32%).

3-*O*-Ethyl *α*-Mangostin (**9**): Yield 10%; yellow amorphous; mp 153–154°C; IR (KBr) cm^{-1}: 3407, 2916, 1640, 1600, 1464, 1426, 1372, 1279, 1215 and 1143; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 1.45 (t, 3H, *J*=6.9 Hz, $OCH_2C\underline{H}_3$), 1.65 and 1.66 (each s, each 3H, H-14, H-19), 1.78 and 1.81 (each s, each 3H, H-15, H-20), 3.34 (d, 2H, *J*=7.1 Hz, H-11), 3.78 (s, 3H, OCH_3), 4.07 (d, 2H, *J*=5.8 Hz, H-16), 4.07 (q, 2H, *J* =6.9 Hz, $OC\underline{H}_2CH_3$), 5.24 (m, 2H, H-12, H-17), 6.28 (s, 1H, H-4), 6.30 (brs, 1H, 6-OH), 6.80 (s, 1H, H-5) and 13.94 (s, 1H, 1-OH); HR-FAB-MS *m/z*: 439.2123 $[M+H]^+$ (Calcd for $C_{26}H_{30}O_6$+H: 439.2120).

3-*O*-Ethyltetrahydro *α*-Mangostin (**25**): **25** was prepared in a similar manner as for Compound **9**, but using tetrahydro *α*-mangostin in place of *α*-mangostin: Yield 4%; pale yellow viscous; IR (neat) cm^{-1}: 3300, 2950, 2865, 1638, 1600, 1466, 1384, 1364, 1285, 1202, 1140, 925 and 813; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.93 (d, 6H, *J*=6.0 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.0 Hz, H-19, H-20), 1.34–1.55 (m, 4H, H-12, H-17), 1.42 (m, 3H, *J*=6.8 Hz, $OCH_2C\underline{H}_3$), 1.60 (m, 1H, H-13), 1.73 (m, 1H, H-18), 2.63 (brt, 2H, *J*=7.7 Hz, H-11), 3.31 (brt, 2H, *J*=8.0 Hz, H-16), 3.81 (s, 3H, 7-OCH_3), 4.08 (q, 2H, *J*=6.0 Hz, $OC\underline{H}_2CH_3$), 6.25 (s, 1H, 6-OH), 6.28 (s, 1H, H-4), 6.78 (s, 1H, H-5) and 13.57 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 441.2280 $[M-H]^-$ (Calcd for $C_{26}H_{34}O_6$−H: 441.2283).

Tetrahydro *α*-Mangostin-3-*O*-acetate (**42**): Compound **42** was prepared in a similar manner as for **9**, but using acetic anhydride and acetone in place of diethyl sulfate and DMF: Yield 32%; yellow amorphous; mp 170–171°C; IR (KBr) cm^{-1}: 3346, 2963, 2932, 1728, 1640, 1619, 1579, 1471, 1437, 1373, 1284, 1258, 1206, 1117, 1036, 844 and 830; ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ*: 0.79 (d, 6H, *J*=6.1 Hz, H-14, H-15), 0.84 (d, 6H, *J*=5.8 Hz, H-19, H-20), 1.26 (m, 4H, H-12, H-17), 1.45 (m, 1H, H-13), 1.60 (m, 1H, H-18), 2.20 (s, 3H, $COCH_3$), 2.40 (brt, 2H, *J*=7.2 Hz, H-11), 3.16 (brt, 2H, *J*=7.0 Hz, H-16), 3.91 (s, 3H,

7-OCH_3), 6.40 (s, 1H, H-4), 6.63 (s, 1H, H-5), 9.85 (brs, 1H, 6-OH), and 13.82 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 457.2224 $[M+H]^+$ (Calcd for $C_{26}H_{32}O_7$+H: 457.2220).

Hydrogenation of α-Mangostin (1) and Compound 31 A mixture of α-mangostin (**1**) (0.5 g, 1.21 mmol) and Pd–C in MeOH (5 mL) was stirred under H_2 atmosphere for 6 h. The catalyst was filtered off through a Celite pad, and MeOH was removed and then crystallized from acetone–hexane.

Tetrahydro α-Mangostin (**15**): Yield 98%; pale yellow needles; mp 128–130°C; IR (KBr) cm^{-1}: 3475, 3203, 2953, 1646, 1608, 1467, 1206, 1122, 1067, 980 and 820; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.95 (d, 6H, *J*=6.8 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.8 Hz, H-19, H-20), 1.40 (m, 2H, H-12), 1.45 (m, 2H, H-17), 1.62 (m, 1H, H-13), 1.73 (m, 1H, H-18), 2.63 (t, 2H, *J*=8.0 Hz, H-11), 3.30 (t, 2H, *J*=8.0 Hz, H-16), 3.81 (s, 3H, 7-OCH_3), 5.72 (brs, 1H, 3-OH), 6.22 (s, 1H, H-4), 6.34 (brs, 1H, 6-OH), 6.75 (s, 1H, H-5) and 13.84 (s, 1H, 1-OH); HR-FAB-MS *m/z*: 415.2121 $[M+H]^+$ (Calcd for $C_{25}H_{30}O_6$+H: 415.2120).

6-*O*-Propyltetrahydro α-Mangostin (**33**): Compound **33** was prepared in a similar manner as for **15**, but using compound **31** in place of **15**: Yield 84%; yellow amorphous; mp 143–145°C; IR (KBr) cm^{-1}: 3312, 2954, 2869, 1645, 1605, 1588, 1463, 1285, 1196, 1124, 1038 and 824; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.95 (d, 6H, *J*=6.6 Hz, H-14, H-15), 0.99 (d, 6H, *J*=6.3 Hz, H-19, H-20), 1.09 (t, 3H, *J*=7.2 Hz, OCH_2–CH_2–$C\underline{H}_3$), 1.43 (m, 4H, H-12, H-17), 1.59 (m, 1H, H-13), 1.76 (m, 1H, H-18), 1.93 (m, 2H, OCH_2–$C\underline{H}_2$–CH_3), 2.65 (brt, 2H, *J*=7.6 Hz, H-11), 3.34 (brt, 2H, *J*=7.8 Hz, H-16), 3.81 (s, 3H, 7-OCH_3), 4.04 (t, 2H, *J*=6.2 Hz, $OC\underline{H}_2$–CH_2–CH_3), 6.22 (s, 1H, H-4), 6.68 (s, 1H, H-5) and 13.90 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 457.2587 $[M+H]^+$ (Calcd for $C_{27}H_{32}O_6$+H: 457.2585).

Demethylation of 3,6-di-*O*-Methyltetrahydro α-Mangostin (17) A mixture of compound **17** (0.58 g, 1.31 mmol), morpholine (8 mL) and water (2 mL) in a sealed tube was purged with nitrogen gas and then heated at 140°C in an oil bath for 4 d (for compound **18**) and at 170°C for 5 d (for compounds **19** and **20**). The reaction mixture was cooled and poured into an ice-cold dilute HCl and then extracted with EtOAc. The combined organic phase was washed with H_2O, dried over anhydrous Na_2SO_4, the solvent was then evaporated and the residue chromatographed using hexane–acetone (8.5 : 1.5).

3-*O*-Methyltetrahydro-α-mangostin (**18**): Yield 10%; yellow amorphous; mp 179–180°C; IR (KBr) cm^{-1}: 3419, 2954, 2867, 1651, 1598, 1462, 1289, 1202, 1141, 1090 and 846; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.93 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.4 Hz, H-19, H-20), 1.57 (m, 4H, H-17, H-18), 1.73 (m, 1H, H-13), 2.62 (t, 2H, *J*=7.5 Hz, H-11), 3.31 (t, 2H, *J*=7.5 Hz, H-16), 3.82 and 3.87 (each s, each 3H, 7-, 3-OCH_3, respectively), 6.30 (s, 2H, H-4, 3-OH), 6.78 (s, 1H, H-5) and 13.56 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 427.2124 $[M-H]^-$ (Calcd for $C_{25}H_{32}O_6$−H: 427.2126).

Tetrahydro γ-Mangostin (**19**): Yield 20%; yellow amorphous; mp 180–182°C; IR (KBr) cm^{-1}: 3592, 3548, 3160, 2953, 2868, 1649, 1619, 1462, 1358, 1297, 1203, 1120 and 842; ^{1}H-NMR ($CDCl_3$+CD_3OD, 300 MHz) δ: 0.83 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.97 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.42 (m, 4H, H-12, H-17), 1.60 (m, 1H, H-13), 1.71 (m, 1H, H-18), 2.60 (t, 2H, *J*=7.5 Hz, H-11), 3.13 (t, 2H, *J*=7.7 Hz, H-16), 6.13 (s, 1H, H-4), 6.58 (s, 1H, H-5) and 13.87 (brs, 1H, 1-OH); HR-TOF-MS *m/z*: 399.1801 $[M-H]^-$ (Calcd for $C_{23}H_{28}O_6$−H: 399.1813).

3-*O*-Methyltetrahydro γ-Mangostin (**20**): Yield 14%; yellow amorphous; mp 179–180°C; IR (KBr) cm^{-1}: 3492, 3236, 2953, 1646, 1616, 1484, 1289, 1213, 1138 and 841; ^{1}H-NMR ($CDCl_3$+accetone-d_6, 300 MHz) δ: 0.89 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.94 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.32 (m, 2H, H-12), 1.42 (m, 2H, H-17), 1.54 (m, 1H, H-13), 1.69 (m, 1H, H-18), 2.58 (t, 2H, *J*=7.7 Hz, H-11), 3.32 (t, 2H, *J*=8.1 Hz, H-16), 3.81 (s, 3H, 3-OCH_3), 5.91 (brs, 1H, 7-OH), 6.22 (s, 1H, H-4), 6.71 (s, 1H, H-5), 8.83 (brs, 1H, 6-OH) and 13.70 (brs, 1H, 1-OH); HR-TOF-MS *m/z*: 413.1972 $[M-H]^-$ (Calcd for $C_{24}H_{30}O_6$−H: 413.1970).

Methylation of Tetrahydro γ-Mangostin (19) Methyl iodide (19.8 mg, 0.14 mmol) was added to a solution of **19** (30.1 mg, 0.07 mmol) in acetone (1.5 mL) and K_2CO_3 (9.6 mg, 0.07 mmol). After stirring for 12 h at 5–10°C, the reaction mixure was quenched with ethyl acetate and water, then extracted with ethyl acetate (3×100 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 9.2 : 0.8 v/v hexane–acetone to afford product **21**, **22** and the fully methylated compound **17**.

6-*O*-Methyltetrahydro γ-Mangostin (**21**): Yield 12%, yellow amorphous; mp 176–178°C; IR (KBr) cm^{-1}: 3446, 2954, 2870, 1642, 1614, 1461, 1439, 1283, 1209, 1122 and 821; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.95 (d, 6H, *J*=6.9 Hz, H-14, H-15), 0.97 (d, 6H, *J*=7.0 Hz, H-19, H-20), 1.43 (m, 4H, H-12, H-17), 1.64 (m, 1H, H-13), 1.71 (m, 2H, H-18), 2.63 (dt, 2H, *J*=5.7, 8.0 Hz, H-11), 3.36 (dt, 2H, *J*=5.3, 8.3 Hz, H-16), 3.97 (s, 3H, 6-OCH_3), 5.56 (brs, 1H, 7-OH), 6.22 (s, 1H, H-4), 6.68 (s, 1H, H-5) and 13.91 (s, 1H, 1-OH); HR-TOF-MS *m/z*: 413.1961 $[M-H]^-$ (Calcd for $C_{24}H_{30}O_6$−H: 413.1970).

3,6-di-*O*-Methyltetrahydro γ-Mangostin (**22**): Yield 47%; yellow amorphous; mp 172–173°C; IR (KBr) cm^{-1}: 3591, 3548, 3158, 2953, 2870, 1649, 1618, 1583, 1460, 1296, 1204, 1122 and 835; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.93 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.98 (d, 6H, *J*=6.5 Hz, H-19, H-20), 1.36 (brq, 2H, *J*=7.8 Hz, H-12), 1.44 (brq, 2H, *J*=8.0 Hz, H-17), 1.54 (m, 1H, H-13), 1.72 (m, 2H, H-18), 2.62 (dt, 2H, *J*=5.7, 7.8 Hz, H-11), 3.36 (dt, 2H, *J*=5.3, 8.0 Hz, H-16), 3.86 (s, 3H, 3-OCH_3), 3.98 (s, 3H, 6-OCH_3), 6.27 (s, 1H, H-4), 6.69 (s, 1H, H-5) and 13.75 (brs, 1H, 1-OH); HR-TOF-MS *m/z*: 427.2122 $[M-H]^-$ (Ccalcd for $C_{25}H_{32}O_6$−H: 427.2126).

Preparation of 1-Methoxytetrahydro α-Mangostin (23) Compound **15** (337 mg, 0.81 mmol) was dissolved in acetone (40 mL), K_2CO_3 (112 mg, 0.81 mmol) was added with stirring for 5 min and then tosyl chloride (232 mg, 1.21 mmol) was added. The solution was stirred for 1 h and the solvent was removed under reduced pressure. The reaction mixture was added with water and extracted with EtOAc (3×30 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane–acetone (9.5 : 0.5) to give **23a**.

Tetrahydro α-Mangostin-3,6-di-*O*-tosylate (**23a**): Yield 96%; yellow amorphous; mp 119–121°C; IR (KBr) cm^{-1}: 3446, 2956, 2869, 1638, 1620, 1597, 1461, 1425, 1283, 1195, 1178–1146, 1050, 817 and 742; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.85 (d, 6H, *J*=6.5 Hz, H-14, H-15), 0.92 (d, 6H, *J*=6.6 Hz, H-19, H-20), 1.23 (m, 4H, H-12, H-17), 1.48 (m, 1H, H-13), 1.62 (m, 1H, H-18), 2.41 (brt, 2H, *J*=8.0 Hz, H-11), 2.44 (s,

3H, 6-$OSO_2C_6H_4$–CH_3), 2.46 (s, 3H, 3-$OSO_2C_6H_4$–CH_3), 3.21 (brt, 2H, J=8.4 Hz, H-16), 3.69 (s, 3H, 7-OCH_3), 6.79 (s, 1H, H-4), 7.24 (s, 1H, H-5), 7.31 (d, 2H, J=8.1, ArH), 7.35 (d, 2H, J=8.2 Hz, ArH), 7.76 and 7.80 (each d, each 2H, each J=8.3 Hz, ArH), 13.41 (s, 1H, 1-OH); ESI-MS m/z: 721 $[M-H]^-$.

Methylation of Compound **23a**: Compound **23a** (66 mg, 0.09 mmol) was dissolved in DMF (2 mL) and K_2CO_3 (60 mg) and methyl iodide (0.5 mL) was added. The reaction mixture was stirred for 3 h, water was added and the mixture was extracted with EtOAc. The combined organic phase was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography eluting with hexane–acetone (9.8 : 0.2) to yield **23b**.

1-Methoxy-tetrahydro α-Mangostin-3,6-di-*O*-tosylate (**23b**): Yield 87%; colorless amorphous; mp 101–103°C; IR (KBr) cm^{-1}: 3447, 2954, 2869, 1661, 1569, 1455, 1423, 1379, 1269, 1259, 1194, 1112, 1091, 1051, 865, 817 and 739; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.87 (d, 6H, J=6.6 Hz, H-14, H-15), 0.94 (d, 6H, J=6.5 Hz, H-19, H-20), 1.25 (m, 2H, H-12, H-17), 1.26 (m, 1H, H-13), 1.68 (m, 1H, H-18), 2.44 (brt, 2H, J=8.4 Hz, H-11), 2.46 (s, 3H, 6-$OSO_2C_6H_4$–CH_3), 2.48 (s, 3H, 3-$OSO_2C_6H_4$–CH_3), 3.21 (brt, 2H, J=8.0 Hz, H-16), 3.70 (s, 3H, 7-OCH_3), 3.84 (s, 3H, 1-OCH_3), 7.12(s, 1H, H-4), 7.22 (s, 1H, H-5), 7.33 and 7.38 (each d, each 2H, each J=8.0 Hz, Ar-H), 7.79 and 7.82 (each d, each 2H, each J=8.3 Hz, Ar-H); ESI-MS m/z: 737 $[M+H]^+$.

Hydrolysis of Compound **23b**: To a solution of **23b** (60 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was added ethanolic–KOH solution (5%, 1 mL) and the mixture was stirred at rt for 2 h. The suspension was acidified with 10% HCl to pH 7 and then water was added and the mixture was extracted with EtOAc. The combined organic phase was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with hexane–acetone (9.8 : 0.2) to give the targeted product.

1-Methoxytetrahydro α-Mangostin (**23**): Yield 75%; pale yellow amorphous; mp 97–99°C; IR (KBr) cm^{-1}: 3297, 2954, 2868, 1607, 1462, 1429, 1382, 1275, 1206, 1124, 1074, 1037 and 836; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.90 (d, 6H, J=6.6 Hz, H-14, H-15), 0.95 (d, 6H, J=6.6 Hz, H-19, H-20), 1.38 (m, 2H, H-12), 1.45 (m, 2H, H-17), 1.60 (m, 1H, H-13), 1.74 (m, 1H, H-18), 2.62 (brt, 2H, J=8.2 Hz, H-11), 3.35 (brt, 2H, J=7.9 Hz, H-16), 3.80 (s, 3H, 7-OCH_3), 3.85 (s, 3H, 1-OCH_3), 6.53 (s, 1H, H-4), 6.66 (s, 1H, H-5); HR-TOF-MS m/z: 427.2110 $[M-H]^-$ (Calcd for $C_{25}H_{32}O_6-H$: 427.2126).

Antimycobacterial Assay The *in vitro* antimycobacterial activities were carried out according to the procedures described previously using microplate Alamar blue assay (MABA) with NIH, RMP and kanamycin as positive controls.[4,20] Growth of the organisms was determined by visual determination of a color change from blue to pink. The MIC was defined as the lowest concentration which prevented the color change.

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