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The first total synthesis of calabricoside A

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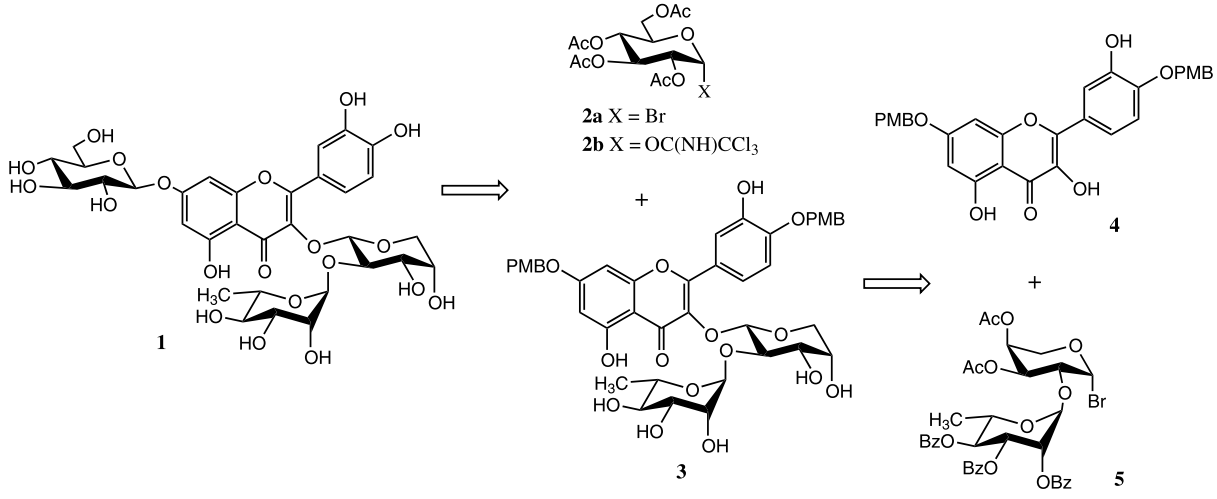
Abstract—Quercetin 3-*O*-[α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside]-7-*O*-β-D-glucopyranoside (calabricoside A), a new flavonol triglycoside isolated from the aerial parts of *Putoria calabrica* showing strong radical scavenging activity, was synthesized through a combination of phase-transfer-catalyzed C-3 glycosylation and AgOTf promoted homogeneous C-7 glycosylation in CH_2Cl_2.

Flavonoid and other polyphenol glycosides are widespread ubiquitous natural product from fruits, vegetables, red wines and teas.[1] Many flavinoids show biological activities important in the growth and development of plants, and more interestingly, represent potential drug candidates having antimicrobial, anticancer and antioxidant properties.[2] Polyphenol-rich diets are often advocated to lower the risk of developing cardiovascular diseases and cancers and some of flavonoid glycosides are currently used for the treatment of various vascular diseases.[3,4] Despite of the wide occurrence and biological importance of flavonol and other polyphenol glycosides, synthetic efforts towards efficient preparation of this group of natural products are surprisingly rarely reported.[5–11] The major challenge for the synthesis of these flavonoid glycosides is that standard high yielding glycosylation reactions, catalyzed by trimethylsilyl triflate (TMSOTf), boron trifluoride etherate ($BF_3{\cdot}Et_2O$) or *N*-iodosuccimidate (NIS), are not generally applicable for the formation of C-3 glycosylated products, as many of these, such as catechin are very sensitive in acidic medium.[12] Furthermore, regioselective glycosylation, especially multi-glycosyl substitution of flavonoids or polyphenols, is often complicated by low yields and multiple stereo chemical outcomes.[10]



Scheme 1. Retrosynthetic analysis.

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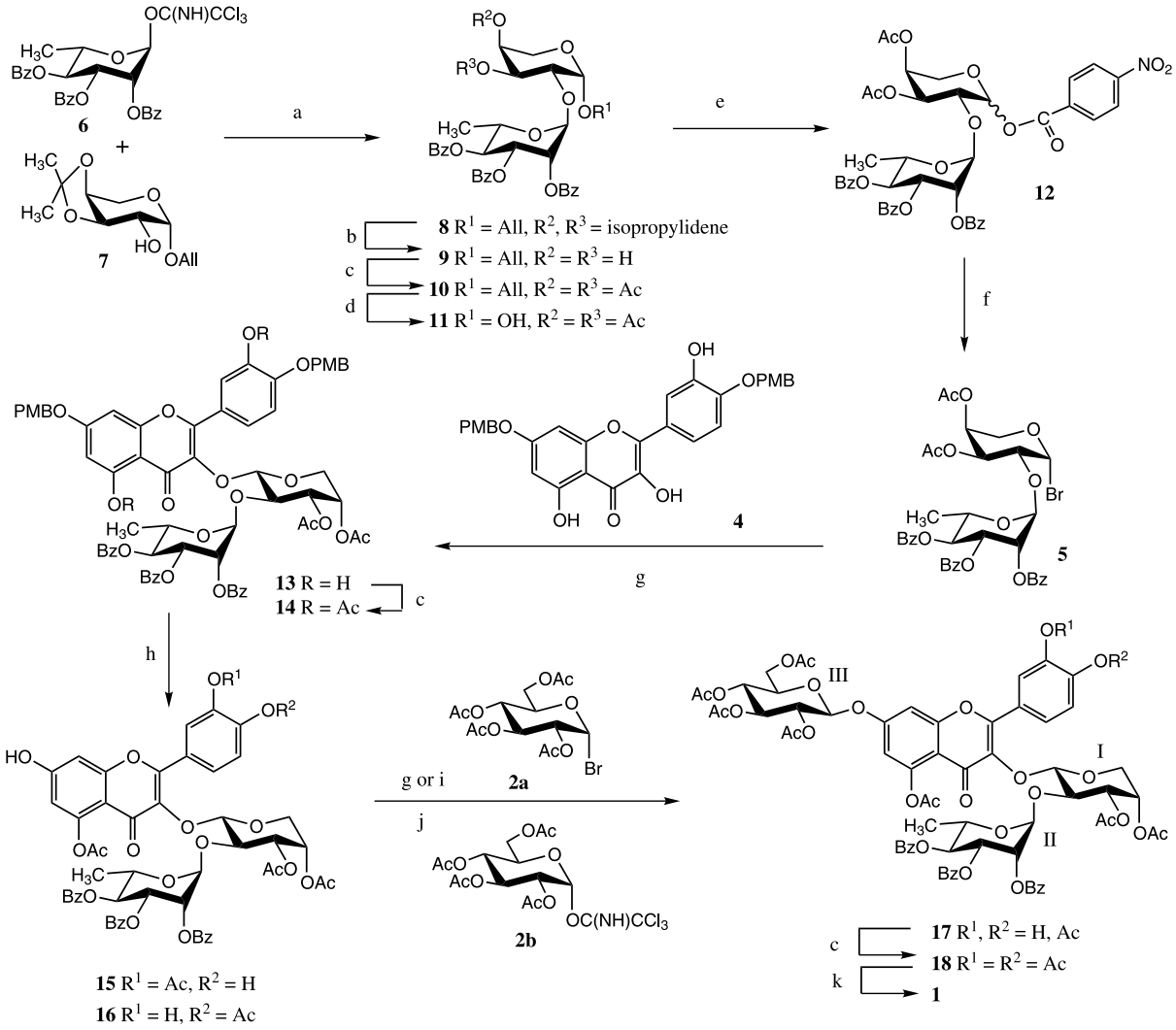
Calabricoside A (quercetin 3-*O*-[α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside]-7-*O*-β-D-glucopyranoside),[13] a new flavonol triglycoside isolated from the aerial parts of *Putoria calabrica*, shows strong radical scavenging activity with an IC_{50} value of 0.25 μM determined by formyl-methionyl-leucyl-phenylalanin (FMLP) stimulated human polymorphonuclear neutrophils (PMNs). Here we describe the first total synthesis of calabricoside A.

We envisioned that calabricoside A (**1**) could be constructed from the easily prepared glucosyl donor **2**, suitably 7,4′-methoxybenzyl (PMB) ether protected quercetin **4** and a disaccharide donor **5** (Scheme 1).

Commercially available quercetin was converted into 7,4′-di-*O*-methoxybenzylated **4** in three steps and in 31% overall yield, employing a similar procedure to that developed by Jurd,[14] i.e. acetylation of quercetin with acetic anhydride in pyridine; regioselective benzylation of C-7 and C-4′ with 4-methoxybenzyl chloride and K_2CO_3 in refluxing acetone; and deacetylation with 10% aqueous NaOH. Disaccharide bromide **5** was prepared through conventional glycosylation and protecting group manipulation (Scheme 2). To this end, rhamnopyranosyl trichloroacetimidate **6**[15] was condensed with allyl 3,4-di-*O*-isopropylidene-β-L-arabinopyranoside (**7**)[16] giving disaccharide **8** in 92% yield. The isopropylidene of **8** was readily cleaved using 80% HOAc in THF at 50°C (→**9**), the free hydroxyl groups were then acetylated with acetic anhydride in pyridine (→**10**). Removal of allyl group from **10** was carried out smoothly with $PdCl_2$ in 90% HOAc–NaOAc system to give hemiacetal **11** in excellent yield (90% from **8**).[17] We then tried to convert **11** to **5** via acetylation (Ac_2O in pyridine) and bromination (HBr in HOAc). However, bromination appeared to be very slow and by-products were observed on TLC when the starting material had been completely consumed, thus only a modest yield of **5** was obtained. To improve the synthesis of **5**, hemiacetal **11** was first transformed into 4-nitrobenzoyl derivative **12** with 4-nitrobenzoyl chlo-



Scheme 2. *Reagents and conditions*: (a) TMSOTf, CH_2Cl_2, 92%; (b) 80% HOAc, THF, 50°C; (c) Ac_2O, Pyr; (d) $PdCl_2$, 90% HOAc, NaOAc, 90% from **8**; (e) *p*-NO_2BzCl, Pyr; (f) HBr, HOAc, 87% from **11**; (g) 0.15 M aq. K_2CO_3, $CHCl_3$, TBAB, 50°C, >78% for **13**; 11% for **17**; (h) $Pd(OH)_2$-C, H_2, 93%; (i) K_2CO_3, DMF, 6%; (j) AgOTf, CH_2Cl_2, 52%; (k) NaOMe, MeOH, 91%.

ride in pyridine, then subjected to bromination, with HBr in HOAc, affording disaccharide bromide **5** was thus furnished in 87% yield from **11**. Phase-transfer-catalyzed (PTC)[8,18] coupling reaction of **5** and **4** was first conducted in 1.25 M aqueous KOH–$CHCl_3$ system at 65°C, gave **13** in 30% yield. Encouraged by a recent report from Han and Yu,[9] **5** and **4** was condensed in 0.15 M aqueous K_2CO_3–$CHCl_3$ system in the presence of tetrabutylammonium bromide (TBAB) at 50°C giving the desired **13** in >78% isolation yield. The proton coupling ($J=6.7$ Hz) observed for the anomeric proton of arabinose residue (δ 5.76 ppm) demonstrates that the disaccharide has the expected α-linkage to the quercetin aglycone.[19] Moreover, the cross peak from arabinosyl H-1 (δ 5.76 ppm) to quercetin C-3 (δ 135.6 ppm) in the HMBC spectra confirmed that the glycosylation took place at the C-3 position of quercetin. No β-anomer was detected under these glycosylation conditions. After acetylation of remaining 5,3′-diol of **13** (→**14**), 7,4′-methoxybenzyl groups were cleanly removed by hydrogenation over 20% $Pd(OH)_2$ on-charcoal in a mixed solvent of ethanol and ethyl acetate (1:1) under atmospheric pressure. Surprisingly, an inseparable mixture (3:1 based on ^{1}H NMR spectra) was isolated in 93% yield. Acetylation of this mixture affording a single compound suggesting that the mixture came from 3′,4′-acetyl migration in the quercetin residue. The ^{1}H NMR spectra showed H-5′ at 6.62 ppm in major fraction while at 7.07 ppm in the minor one, indicating 4′-OAc component **16** is the dominant in the mixture. It was reported that the glycosylation or sulfonation of the catechol moiety makes the residual H-atom (OH-C(3′) or OH-C(4′)) less reactive.[5] We took advantage of this report to directly glycosylate **16**/**15** with donor **2a** under the PTC conditions as described in the preparation of **13**, affording the mixture **17**, which was acetylated giving **18** in a yield of 11%. We rationalized that the poor solubility of **2a** and **16**/**15** in this two-phase solvent system might be responsible for the low glycosylation yield. Thus, the same reaction was conducted in dry DMF with anhydrous K_2CO_3 as base at rt. However, much lower yield of **18** (6%) was obtained, probably due to the easy loss of acetyl groups from flavonoid under these coupling conditions.[20] This reaction could be significantly improved by condensing trichloroacetimidate donor **2b** and **16/15** in CH_2Cl_2 using 1 equiv. of AgOTf catalyst, furnishing **18** in 52% yield after acetylation. The observed $J_{1,2}$ value (8.4 Hz) for the glucose residue in ^{1}H NMR spectra and the cross peak from glucose H-1^{III} (5.31 ppm) to quercetin C-7 (162.5 ppm) in the HMBC spectrum clearly indicates α-glycosylation took place at C-7. Finally, removal of all acyl protection groups using catalytic amount of NaOMe in MeOH followed by purification on Sephadex LH20 using MeOH as eluent furnished target molecule **1** (91%). All the data recorded for **1** were identical to those previously reported.[13]

In summary, we have described the first total synthesis of calabricoside A from 7,4′-di-*O*-methoxybenzyl quercetin in 12 steps and 24.7% overall yield. The phase transfer catalyzed glycosylation of quercetin C-3 was proved to be very efficient using 0.15 M aqueous K_2CO_3 and 1 equiv. of TBAB in chloroform at 50°C, while further glycosylation of C-7 was more practical in CH_2Cl_2 using trichloroacetimidate as donor and AgOTf as catalyst. The present exploration should be valuable to the preparation of multi-glycosylated flavonol glycosides.[21,22]

Acknowledgements

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References

1. Bohm, B. A. *Introduction to Flavonoids*; Harwood Academic Publishers: Amsterdam, 1998.
2. Harborne, J. B.; Baxter, H. *The Handbook of Natural Flavonoids*; John Wiley & Sons: Chichester, 1999; Vol. 1.
3. Harborne, J. B.; Williams, C. A. *Phytochemistry* **2000**, *55*, 481–504.
4. Pietta, P.-G. *J. Nat. Prod.* **2000**, *63*, 1035–1042.
5. Alluis, B.; Dangles, O. *Helv. Chim. Acta.* **2001**, *84*, 1133–1156.
6. Vermes, B.; Chari, V. M.; Wagner, H. *Helv. Chim. Acta.* **1981**, *64*, 1964–1967.
7. Bouktaib, M.; Atmani, A.; Rolando, C. *Tetrahedron Lett.* **2002**, *43*, 6263–6266.
8. Demetzos, C.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M. *Carbohydr. Res.* **1990**, *207*, 131–137.
9. Li, M.; Han, X.; Yu, B. *Tetrahedron Lett.* **2002**, *43*, 9467–9470.
10. O'Leary, K. A.; Day, A. J.; Needs, P. W.; Sly, W. S.; O'Brien, N. M.; Williamson, G. *FEBS Lett.* **2001**, *503*, 103–106.
11. Caldwell, S. T.; Crozier, A.; Hartley, R. C. *Tetrahedron* **2000**, *56*, 4101–4106.
12. Brown, R. T.; Carter, N. E.; Mayalarp, S. P.; Sceinmann, F. *Tetrahedron* **2000**, *56*, 9591–9594.
13. Calis, I.; Heilmann, J.; Tasdemir, D.; Linden, A.; Ireland, C. M.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 961–964.
14. Jurd, L. *J. Org. Chem.* **1962**, *27*, 1294–1297.
15. Zhang, M.; Du, Y.; Kong, F. *Carbohydr. Res.* **2001**, *330*, 319–324.
16. Gu, G.; Du, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2075–2079.
17. Du, Y.; Pan, Q.; Kong, F. *Synlett* **1999**, 1648–1649.
18. Jensen, K. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2219–2233.
19. Physical data for some new compounds. **8**: $[\alpha]_D^{25}$ +139° (*c* 1, $CHCl_3$); 1.33 (d, 3 H, *J* 6.2 Hz, H-6^{II}), 1.37, 1.55 (2 s, 6 H, 2 CH_3), 3.87 (dd, 1 H, *J* 3.4, 8.0 Hz, H-2^{I}), 4.00–4.07 (m, 3 H), 4.22–4.31 (m, 3 H), 4.44 (dd, 1 H, *J* 5.6, 8.0 Hz, H-3^{I}), 4.98 (d, 1 H, *J* 3.4 Hz, H-1^{I}), 5.27–5.31 (m, 1 H, CH_2=CH-CH_2-), 5.33 (d, 1 H, *J* 1.6, H-1^{II}), 5.41–5.46 (dd, 1 H, CH_2=CH-CH_2-), 5.64 (t, 1 H, *J* 10.0 Hz, H-4^{II}), 5.79 (dd, 1 H, *J* 1.6, 3.5 Hz, H-2^{II}), 5.88 (dd, 1 H, *J* 3.5, 10.0 Hz, H-3^{II}), 5.96–6.06 (m, 1 H, CH_2=C*H*-CH_2-), 7.24–8.11 (m, 15 H, Ph). **13**: $[\alpha]_D^{25}$ −23°(*c* 0.3, $CHCl_3$); 1.12 (d, 3 H, *J* 6.4 Hz, H-6^{II}), 2.12, 2.23 (2 s, 6 H, 2 Ac), 3.60 (dd, 1 H,

J 1.5, 12.9 Hz, H-5a^{I}), 3.82, 3.83 (2 s, 6 H, 2 CH_3O), 3.86 (dd, 1 H, *J* 3.2, 12.9 Hz, H-5b^{I}), 4.28 (dd, 1 H, *J* 6.7, 9.6 Hz, H-2^{I}), 4.68–4.73 (m, 1 H, H-5^{II}), 5.06 (s, 2 H, $MeOPhCH_2$), 5.08, 5.12 (2 d, 2 H, *J* 12.8 Hz, $MeOPhCH_2$), 5.20 (dd, 1 H, *J* 9.6, 3.5 Hz, H-3^{I}), 5.25–5.28 (m, 1 H, H-4^{I}), 5.35 (d, 1 H, *J* 1.1 Hz, H-1^{II}), 5.60 (dd, 1 H, *J* 1.1 Hz, H-2^{II}), 5.66 (t, 1 H, *J* 9.6 Hz, H-4^{II}), 5.73 (br s, 1 H, 3′-OH), 5.76 (d, 1 H, *J* 6.7 Hz, H-1^{I}), 5.97 (dd, 1 H, *J* 3.3, 9.6 Hz, H-4^{II}), 6.45 (d, 1 H, *J* 2.1 Hz, H-6), 6.50 (d, 1 H, *J* 2.1 Hz, H-8), 6.92–6.96 (m, 4 H, Ar), 7.02 (d, 1 H, *J* 9.5 Hz, H-5′), 7.23–7.60 (m, 13 H, Ar), 7.67 (dd, 1 H, *J* 2.0, 9.5 Hz, H-6′), 7.84–8.10 (m, 7 H, H-2′ and Ar), 12.65 (s, 1 H, 5-OH). MALDITOF-MS Calcd for $C_{67}H_{60}O_{22}$: 1216.36; Found 1239 $(M+Na)^+$. **16**: 1.26 (d, 3 H, *J* 6.3 Hz, H-6^{II}), 2.07, 2.23, 2.28, 2.50 (4 s, 12 H, 4 Ac), 3.66 (dd, 1 H, *J* 1.0, 12.4 Hz, H-5a^{I}), 3.85 (dd, 1 H, *J* 2.1, 12.4 Hz, H-5b^{I}), 4.24 (dd, 1 H, *J* 7.0, 9.3 Hz, H-2^{I}), 4.78, 4.85 (m, 1 H, H-5^{II}), 5.22 (dd, 1 H, *J* 3.5, 9.3 Hz, H-3^{I}), 5.27 (br s, 1 H, H-4^{I}), 5.37 (d, 1 H, *J* 1.0 Hz, H-1^{II}), 5.63 (dd, 1 H, *J* 1.0, 3.3 Hz, H-2^{II}), 5.71 (d, 1 H, *J* 7.0 Hz, H-1^{I}), 5.73 (t, 1 H, *J* 10.1 Hz, H-4^{II}), 6.02 (dd, 1 H, *J* 3.3, 10.1 Hz, H-3^{II}), 6.37 (d, 1 H, *J* 1.9 Hz, H-6), 6.50 (d, 1 H, *J* 1.9 Hz, H-8), 6.62 (d, 1 H, *J* 8.4 Hz, H-5′), 7.24–8.13 (m, 17 H, H-2′,6′ and Ar). MALDITOF-MS Calcd for $C_{55}H_{48}O_{22}$: 1060.26; Found 1083 $(M+Na)^+$. **18**: $[\alpha]_D^{25}$ −38° (*c* 1.6, $CHCl_3$); 1.15 (d, 3 H, 6.3 Hz, H-6^{II}), 2.03, 2.05, 2.06, 2.07, 2.08, 2.21, 2.27, 2.34, 2.47 (9 s, 27 H, 9 Ac), 3.55 (dd, 1 H, *J* 1.0, 12.9 Hz, H-5a^{I}), 3.78 (dd, 1 H, *J* 3.0, 12.9 Hz, H-5b^{I}), 3.91–3.94 (m, 1 H, H-5^{III}), 4.11 (dd, 1 H, *J* 7.1, 9.2 Hz, H-2^{I}), 4.15 (dd, 1 H, *J* 2.4, 12.4 Hz, H-6a^{III}), 4.30 (dd, 1 H, *J* 5.0, 12.4 Hz, H-6b^{III}), 4.70–4.75 (m, 1 H, H-5^{II}), 5.14–5.20 (m, 3 H, H-2^{III}, H-4^{III}, H-3^{I}), 5.23 (br s, 1 H, H-4^{I}), 5.29 (d, 1 H, *J* 1.3 Hz, H-1^{II}), 5.31 (d, 1 H, *J* 8.4 Hz, H-1^{III}), 5.34 (t, 1 H, *J* 9.3 Hz, H-3^{III}), 5.56–5.59 (m, 2 H, *J* 7.1, 1.3, 3.6 Hz, H-1^{I} and H-2^{II}), 5.69 (t, 1 H, *J* 10.0 Hz, H-4^{II}), 5.96 (dd, 1 H, *J* 3.6, 10.0 Hz, H-3^{II}), 6.85 (d, 1 H, *J* 2.1 Hz, H-6), 7.10–8.11 (m, 19 H, H-8, H-5′, H-2′, H-6′ and Ar). MALDITOF-MS Calcd for $C_{71}H_{68}O_{32}$: 1432.4; Found 1455.3 $(M+Na)^+$. **1**: $[\alpha]_D^{25}$ −129° (*c* 1, MeOH); 1.07 (d, 1 H), 3.35–3.55 (m, 6 H), 3.68–3.95 (m, 8 H), 4.12 (dd, 1 H, *J* 6.3, 7.4 Hz, H-2^{II}), 5.06 (d, 1 H, *J* 8.0 Hz, H-1^{III}), 5.10 (br s, 1 H, H-1^{II}), 5.59 (d, 1 H, *J* 6.3 Hz, H-1^{I}), 6.48, 6.74 (2 d, 2 H, *J* 1.6 Hz, H-6, H-8), 6.90 (d, 1 H, *J* 8.3 Hz, H-5′), 7.59 (dd, 1 H, *J* 2.0, 8.3 Hz, H-6′), 7.66 (d, 1 H, *J* 2.0 Hz, H-2′); ^{13}C NMR (CD_3OD): 17.4, 62.1, 65.5, 68.5, 70.0, 71.2, 72.3 (2 C), 73.0, 74.0, 74.5, 77.1, 77.8, 78.2, 96.2, 100.9, 101.3, 101.8, 102.4, 107.5, 116.4, 117.0, 123.1 (2 C), 135.5, 146.1, 150.0, 157.9, 158.6, 163.0, 164.8, 179.7. MALDITOF-MS Calcd for $C_{32}H_{38}O_{20}$: 742.2; Found 765 $(M+Na)^+$, 781 $(M+K)^+$.

20. Chakraborti, A. K.; Nayak, M. K.; Sharma, L. *J. Org. Chem.* **1999**, *61*, 8027–8030.
21. Murakami, T.; Kohno, K.; Ninomiya, K.; Matsuda, H.; Yoshikawa, M. *Chem. Pharm. Bull.* **2001**, *49*, 1003–1008.
22. Gunasegaran, R.; Subramani, K.; Parimala, P. A.; Nair, A. G. R.; Rodriguez, B.; Madhusudanan, K. P. *Fitoterpia* **2001**, *72*, 201–205.