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Tonkinenin A. A New Polyoxygenated Cyclohexane Derivative from *Uvaria tonkinensis*

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Abstract: The ethanolic extract of the seeds of *Uvaria tonkinensis* (Annonaceae), collected on Hainan Island, have led to the isolation of a new polyoxygenated cyclohexane derivative tonkinenin A [**1**]. The structure of **1** was deduced from spectroscopic characteristics and the absolute stereochemistry assigned by the *O*-methylmandelate ester method. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Annonaceae is a large family of subtropical trees and shrubs comprising about 120 genera and more than 200 species.[1] The Annonaceous acetogenins have attracted considerable attention since the report of the antitumor uvaricin in 1982 from *Uvaria accumnata*,[2] and more recent work notably by McLaughlin and coworkers.[3] The *Uvaria* genus, widely distributed across Asia, Africa, and Australia,[4] with ten species known to occur in southern China, is well-known for both Annonaceous acetogenins as well as polyoxygenated cyclohexane derivatives.[4,5] Both *U. macrophylla*[6] and *U. tonkinensis* [7] are used in Chinese traditional medicine to treat digestive disorders. In the course of our investigation into the chemistry of the seeds of this latter species, a new polyoxygenated cyclohexenone derivative **1**, which we have called tonkinenin A, was isolated from the ethanolic extract by standard procedures, and its structure is reported herein.

RESULTS AND DISCUSSION

Chromatography of the crude ethanolic extract of the pulverized seeds of *U. tonkinensis* on silica gel followed by recrystallization gave crystals of **1**. The relatively simple ^{1}H NMR, ^{1}H,^{1}H-COSY, ^{13}C NMR and HMQC spectra of **1** immediately suggested the presence of the two benzoate ester spin systems, a (*Z*)-olefin (J = 10.2 Hz) in an α,β-unsaturated carbonyl subunit, two oxygenated methine and one oxygenated methylene carbons as well as two exchangeable proton resonances presumably due to two alcohols (Table 1). Two distinct low-field ortho-coupled doublet of doublets integrating to 2 protons each, typical of benzoate 2,6-protons, with both showing additional, weak meta-coupling, were well-resolved: δ 8.01 (dd, J = 7.7, 1.6 Hz, H2'/6'), 7.93 (dd, J = 7.7, 1.6 Hz, H2"/6"). The remainder of each benzoate proton spin system showed the four meta protons overlapped, resembling a slightly distorted four proton quartet: δ 7.41 (dd, J = 7.7, 7.6 Hz, H3'/5'), 7.39 (dd, J = 7.7, 7.6 Hz, H3"/5"); similarly the para position protons of the two benzoates also overlapped to appear as a distorted two proton quartet: δ 7.56 (tt, J = 7.6, 1.6 Hz, H4'), 7.54 (tt, J = 7.6, 1.6 Hz, H4"). From the COSY spectrum the assignment of each resonance to the individual benzoate system was routine.

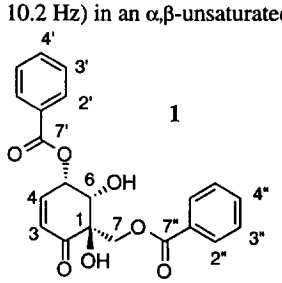

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Table 1. ^{1}H and ^{13}C NMR Data in $CDCl_3$ of **1**.

Position	δ ^{1}H	δ ^{13}C
1	-	77.2
2	-	196.2
3	6.33 (dd, J = 10.2, 0.8 Hz)	128.5
4	6.95 (ddd, J = 10.2, 4.2, 1.5 Hz)	142.7
5	5.93 (ddd, J = 4.2, 3.8, 0.8 Hz)	69.4
6	4.36 (bs, $W_{1/2}$ = 7.5 Hz, $J_{4,5}$ = 3.8 Hz, $J_{3,5}$ = 1.5 Hz)	71.6
7	*proR*: 4.57 (d, J_{AB} = 11.6 Hz) *proS*: 4.84 (d, J_{AB} = 11.6 Hz)	65.4
1'	-	129.1
2', 6'	8.01 (dd, J = 7.7, 1.6 Hz)	129.8
3' 5'	7.41 (dd, J = 7.7, 7.6 Hz)	128.6
4'	7.56 (tt, J = 7.6, 1.6 Hz)	133.8
7'	-	165.3
1"	-	128.7
2", 6"	7.93 (dd, J = 7.7, 1.6 Hz)	129.7
3", 5"	7.39 (dd, J = 7.7, 7.6 Hz)	128.4
4"	7.54 (tt, J = 7.6, 1.6 Hz)	133.4
7"	-	166.2
1-OH	4.01 (s)	-
6-OH	3.08 (bs)	-

The presence of two benzoyl units was also apparent in the mass spectrum (EIMS, 70 eV). The base peak of *m/z* 105 (100%) indicated the phenyl acylium ion, supported by peaks at *m/z* 77 (86%), 122 (59%) and 123 (53%) for the phenyl cation radical, the benzoic acid radical cation and protonated benzoic acid cation, respectively.[8] Sequential loss of the benzoate units from the molecular ion (*m/z* 383 $[M+1]^+$, 78%) was indicated by peaks at *m/z* 261 (58%) and 138 (32%).[9]

The UV, IR, and ^{13}C NMR spectra all indicated the presence of the third carbonyl, ultimately shown to be an α,β-unsaturated ketone in a cyclohexenone ring. The UV spectrum (MeOH) showed a strong absorbance at 232 nm (ε 46,900), along with two weak, broad absorbances: 275 nm (ε 2,600) and 315 nm (ε 1,200), the former presumably arising from the $^{1}L_b$ transition of the benzoate chromophores,[10] and the latter absorbance being typical of the n → π* transition of an enone.[11] A broad absorbance centered at 1700 cm^{-1} in the IR spectrum was resolved, albeit poorly, into three maxima at 1716, 1703, and 1694 cm^{-1}. The latter band is typical of an α,β-unsaturated ketone as in a cyclohexenone.[12] Finally, in the ^{13}C NMR spectrum three carbonyl resonances were observed, two for the benzoate esters (δ 165.3, C7', and 166.2, C7"), and the third at δ 196.2, typical of an α,β-unsaturated ketone. Of note, the α,β-unsaturated ketone chromophore in a cyclohexenone would be expected to have a λ_{max} at approximately the same wavelength as the $^{1}L_a$ transition of the benzoate ester chromophores (232 nm), thus accounting for the large molar extinction coefficient for this band.

In addition to the aromatic and carbonyl resonances of the benzoate and ketone units, the ^{13}C NMR spectrum showed two additional sp^2 carbons at δ 142.7 and 128.5 which correlated with vinyl protons at δ 6.95 (ddd, J = 10.2, 4.2, 1.5 Hz, H4) and 6.33 (dd, J = 10.2, 0.8 Hz, H3), respectively. In a selective INEPT (SINEPT) experiment, saturation of the low field vinyl proton resonance (H4) resulted in a polarization transfer to the ketone carbonyl resonance (C2: δ 196.2) as expected for an α,β-unsaturated ketone. A polarization transfer was also observed to a methine resonance (δ 71.6) ultimately assigned to C6 in this spectrum. The HMBC

experiments distinguished the benzoate carbonyl carbons C7' and C7" (via coupling with H2' and H2" protons, respectively) and C1' and C1" (via coupling with H3', and H3", respectively) of the respective benzoate rings.

The two benzoate units and the α,β-unsaturated ketone accounted for twelve of the thirteen units of unsaturation required by the molecular formula. The remaining unit of unsaturation must therefore be a ring. The presence of two alcohol groups was initially suggested by the appearance of two resonances in the ^{1}H NMR spectrum which exchanged for deuterium upon addition of D_2O: δ 4.01 (s, 1-OH) and 3.08 (s, 6-OH). In addition, the IR spectrum showed a typical ν_{OH} stretching band at 3423 cm^{-1}, while the EIMS showed the loss of a water molecule from the molecular ion at *m/z* 365 ([(M+1)-H_2O]$^+$, 84%), though the fragment corresponding to the loss of the second water molecule was weak: *m/z* 347 ([(M+1)-2H_2O]$^+$, 4%).

From the chemical shifts and molecular formula, the four remaining carbons are sp^3-hybridized oxygenated carbons: two must bear the benzoate ester groups and the other two must be carbinol carbons. The multiplicity of these four carbons, easily deduced from the HMQC experiment, dictates two methines, one methylene, and one quaternary carbon. The ^{1}H,^{1}H-COSY spectrum revealed the H3 - H6 spin system with H5 (δ 5.93, ddd) showing vicinal coupling to the H4 vinyl proton ($J_{4,5}$ = 4.2 Hz), allylic coupling to H3 ($J_{3,5}$ = 0.8 Hz) as well as coupling with H6 ($J_{5,6}$ = 3.8 Hz). In addition to coupling with H5, the H6 resonance (δ 4.36, bs, $W_{1/2}$ = 7.5 Hz) showed W-type coupling to H4 ($J_{4,6}$ = 1.5 Hz) as well as weak coupling with one of the OH hydroxyl protons (δ 3.08, bs, coupling visible in the ^{1}H,^{1}H-COSY and long range COSY [LRCOSY] spectra: Δ = 0.3 s) though inducing no observable splitting, thereby locating one of the two alcohols at C6. This conclusion was supported by the observation of three bond heteronuclear coupling in the HMBC experiment (optimized for $^3J_{C,H}$ = 7 Hz) from this hydroxyl proton to C5. Location of one benzoate ester at C5, suggested by the low field chemical shift of the methine proton, was established by HMBC experiments which showed three bond coupling from H5 to the carbonyl carbon of one benzoate group (δ 165.3, C7'). The HMQC experiment enabled assigned of C5 (δ 69.4) and C6 (δ 71.7).

The two remaining oxygenated carbons must be the methylene (δ 65.4) and quaternary carbons (δ 77.2). The methylene protons formed an AB-system in the ^{1}H NMR spectrum (δ 4.84 and 4.57, J_{AB} = 11.6 Hz) which weakly coupled (LRCOSY only) with the second hydroxyl proton (δ 4.01). Location of the second benzoate ester on this methylene carbon, suggested by the relatively low field shift of the AB-system, was confirmed by the HMBC spectrum which showed coupling between both methylene protons and the second benzoate carbonyl (δ 166.2, C7"). Since neither one of these protons coupled with any other carbon-bonded proton, this benzoylated primary alcohol group must be next to the tertiary alcohol, which must also complete the cyclohexenone ring. Long range heteronuclear couplings between the hydroxyl proton of the C1-OH to C2, C6, and C7, from both H7a and H7b to C2 and C6, and from H3 and H5 to C1 supported the cyclohexenone structure with the tertiary alcohol at C1 (Table 2).

The relative stereochemistry was suggested by the coupling constants and difference NOE experiments. Allylic coupling between H3 and H5 (^4J = 0.8 Hz), W-coupling between H4 and H6 (^4J = 1.5 Hz), and the coupling constant of 3.8 Hz between H5 and H6 suggested that H5 was pseudoaxial and H6 pseudoequatorial, and thus the C5 and C6 oxygen functionalities are cis. A relatively strong NOE (8%) between H5 and H6 supported this conclusion, as did an NOE (1%) between H6 and the ortho protons of the benzoate ring at C5. Such NOE's, and W-coupling with H4, are reasonable for an equatorially oriented H6, but not an axial H6 (which would not show W-coupling with H4, and would have at best a very weak NOE with a trans-diaxial H5). This H5/H6 cis-stereochemistry is somewhat unusual in such natural cyclohexane derivatives from Annonaceae species (see discussion below), but is further supported by the analysis of the NMR spectra of the gabosine cyclohexenones, structurally related natural products isolated from various *Streptomyces* species.[13] Gabosines with similar cis-oriented diol groups at the γ,δ-position relative to the cyclohexenone invariably showed ^3J values of 3.5 - 4.0 Hz, while those with analogous trans-oriented diols were > 8 Hz.

A relatively strong NOE between H6 and the upfield H7 methylene proton (2.1%), and a much weaker NOE with the more downfield H7 (0.8%), indicated an equatorial orientation for C7, typical for these natural products. This conclusion was supported by an NOE (1%) between H6 and the ortho protons of the benzoate

Table 2. Diagnostic Heteronuclear Couplings and NOE's of **1**.

2- and 3-Bond $^{1}H,^{13}C$-Couplings[a]	NOE's[b]
H3: C1	H3: H4 (16.5%)
H4: C2,[c] C3, C6	H4: H3 (8%), H5 (8%)
H5: C1, C2,[d] C3, C4, C6, C7'	H5: H4 (7%), H6 (6%)
C1-OH: C1, C2, C6	H6: H5 (8%), $H7_{proR}$ (2.1%), $H7_{proS}$ (0.8%), H2' (1%), H2" (1%), 6-OH (12%), 1-OH (1%)
$H7_{proR}$: C1, C2, C6, C7"	$H7_{proR}$: H6 (5%), $H7_{proS}$ (33%), H2" (1%), 1-OH (1%)
$H7_{proS}$: C2, C6, C7"	$H7_{proS}$: $H7_{proR}$ (33%), H2" (4%), 1-OH (6%), 6-OH (3%)
H2': C7'	-
H2": C7"	-
C6-OH: C5	-

(a) From HMBC experiments optimized for $J = 4.5$ and 7.0 Hz; H4 and H5 also from selective INEPT experiments. (b) From DNOE experiments: saturation resonance listed before colon. (c) Observed in selective INEPT experiment only. (d) Four-bond coupling from selective INEPT experiment only.

ring attached to C7. Diagnostic NOE's are also compiled in Table 2.

The relatively large magnetic nonequivalence between the C7 methylene protons ($\Delta\delta = 0.27$ ppm) can be understood from the cyclohexenone conformation described above with hydrogen bonding between the C1-OH and the C7-benzoate carbonyl oxygen. Calculations using Gaussian-92 (RHF/6-31G* level) predicts this to be the minimum energy conformation. The seven-membered ring hydrogen bond, while presumably not very rigid, nevertheless directs one of the C7 methylene protons (the *pro-S* proton, infra vide) toward the cyclohexenone carbonyl oxygen, while the other C7 methylene proton (the *pro-R* proton) is directed toward H-6. In accord with this model, the higher field H7 proton (δ 4.57) showed a stronger NOE with H6 (2.1% vs 0.8%, see Table 2) than the lower field H7 (δ 4.84). The computational structure in this conformation predicts that *pro-R*-H7 lies only 2.48 Å away from H6, while *pro-S*-H7, deshielded by the cyclohexenone carbonyl group, lies 3.57 Å away from H6.

The absolute stereochemistry of **1** was established by the *O*-methylmandelate ester method of Mosher and Trost.[14] Formation of the (*R*)- and (*S*)-*O*-methylmandelate esters **2** and **3** by routine DCC coupling proceeded smoothly, with the acylation being characterized by a large downfield shift of H6 (δ 5.85 in **2**, δ 5.83 in **3** from δ 4.36 in **1**). Prominent differential shielding of corresponding protons in the two esters was recorded for H4 ($\Delta\delta = 0.12$ ppm) and H5 ($\Delta\delta = 0.25$ ppm) with these two protons being shielded in **2** relative to **3**. (Assignment of these proton resonances was routine from the $^{1}H,^{1}H$-COSY spectra.) Complementing these observations of differential shielding, both H7 methylene protons (which lie on the other side of the Mosher-Trost plane from H4 and H5) are both more shielded in **3** relative to **2**. Using NOE's with H6 in both esters to assign *proR*-H7 and *proS*-H7 (the H7 proton with the NOE with H6 is assigned as *proR*-H7 as described above for **1**), the differential shielding can be calculated as *proR*-H7: $\Delta\delta = 0.07$ ppm, and *proS*-H7: $\Delta\delta = 0.53$ ppm. Thus as predicted by the conformational model with the 7-membered ring held by a hydrogen bond between the C1-OH and the C7 benzoate carbonyl, the H7 methylene proton which lies closer to the mandelate subunit experiences the greater differential shielding. Using the Mosher-Trost conformational model (Figure 1), these observed differential shieldings indicate the (1*R*, 5*S*, 6*S*) absolute configuration for **1**.

The differential shielding predicted from this model is also observed at the *o*-position protons of the benzoate rings, which were distinguished from the HMBC and NOE experiments. In the HMBC spectrum of **2**, both H7 protons show 3-bond coupling with the C7" carbonyl carbon which in turn shows 3-bond coupling with its respective *o*-protons; the C7' benzoate carbonyl attached to C5 did not show coupling with H5 in the HMBC experiments (but did in a selective INEPT spectrum), but did show coupling with its respective *o*-protons in these spectra. The observation of an NOE between H5 and the H2'/6' *o*-protons confirmed the benzoate

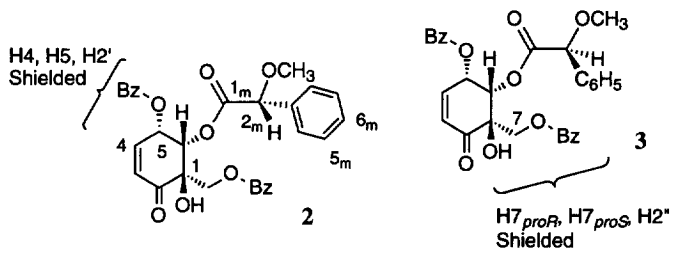
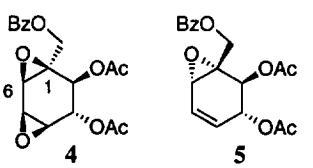


Figure 1. Application of the *O*-methylmandelate ester method for assignment of absolute stereochemistry of **1**.

assignments of **2**. In **3**, the C7' and C7" carbonyls were insufficiently resolved in the HMBC spectrum to allow unambiguous assignment of the benzoate protons by long range heteronuclear coupling with H7 and/or H5. The benzoate systems were distinguished, however, on the basis of NOE's between the H7 protons and H2"/6". With the assignment of the benzoate protons secured, the H2' *o*-protons in **2** were shown to be shielded relative to **3** ($\Delta\delta$ = 0.07 ppm), while the H2" *o*-protons in **3** were slightly shielded relative to those in **2** ($\Delta\delta$ = 0.01 ppm). As a final note in support of this analysis, the $H5_m/7_m$, $H6_m$ overlapped multiplet of the mandelate aromatic ring in **2** was clearly shielded relative to **3** (δ 7.06 vs 7.24). Models shows that in **2**, these protons fall in the shielding cone of the C5 benzoate ring. Similar shielding was not observed in **3** wherein the C7 benzoate ring has significantly less influence on the analogous $H5_m/7_m$, $H6_m$ protons due to hydrogen bonding with the C1-OH which positions this benzoate ring above the mandelate system. The very slight differential shielding observed in the H2"/6" of **2** and **3** ($\Delta\delta$ = 0.01 ppm) in comparison to that of H2'/6' ($\Delta\delta$ = 0.07 ppm) is in accord with this explanation.

The 5,6-cis-dioxygenated relationship of **1**, which has not been previously reported in this class of natural products of plant origin, merits further discussion. The accepted biosynthesis of *Uvaria* polyoxygenated cyclohexane derivatives begins with a stereospecific epoxidation of benzyl benzoate to form an arene oxide, which is subsequently openned to a trans-diol functionality (see Scheme 1).[9a,5a] In support of this hypothesis, benzyl benzoate,[15] and numerous arene oxide-derived intermediates, including the so-called "missing link" cyclohexadienes,[16] with invariant relative and absolute stereochemistry of the 2,3-dioxygenated centers have been reported. In contrast, metabolism of the benzyl benzoate-derived arene oxide or its further metabolized diol proceeds with epoxidation of the 1,6-olefinic subunit with a stereoselectivity that varies, even within the same species.[17] As noted by Thebtaranonth,[5a] this variation accounts for the opposite stereochemistry of the C1 centers in crotepoxide [**4**][18] in comparison to senepoxide[9b] [**5**] and related metabolities in these C1 antipodal series.

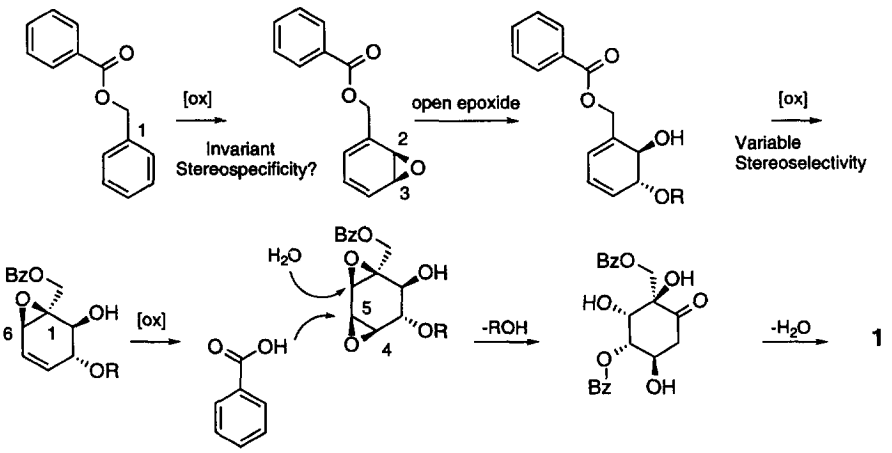


Given the apparently invariant stereospecificity of the initial arene oxide-forming epoxidation of benzyl benzoate, and the overall symmetry of the methylcyclohexane skeleton, the cis relationship of the 5,6-diol functionality in **1** can be reasonably understood as arising from two later oxidation steps (Scheme 1). The stereochemical identity of the initial epoxidation is lost upon transformation to the α,β-unsaturated ketone, and the trans relationship of the C1/C6 oxygen substituents of **1** could in principle arise from openning of a precursor epoxide with an absolute stereochemistry belonging to either the crotepoxide series or the senepoxide series, though the former seems more likely with the more substituted carbon retaining the epoxide oxygen (as illustrated). A third epoxide functionality at C4/C5 with a syn relationship to the C1/C6 epoxide (as found in crotepoxide) could ultimately open to generate the observed C4/C5 cis stereochemistry.

EXPERIMENTAL

General. ^1H and ^{13}C NMR spectra were recorded on a Varian UNITY PLUS 400 (93.94 kG, ^1H 400 MHz, ^{13}C 100 MHz) and a JEOL GSX-270 (63.41 kG, ^1H 270 MHz, ^{13}C 67.5 MHz) in $CDCl_3$ (0.5 mL)

Scheme 1



using 8 mg of **1**, 9 mg of **2** and 10 mg of **3**. The δ 7.24 resonance of residual $CHCl_3$, and the center line of the $^{13}CDCl_3$ triplet (δ 77.0) were used as internal references for the ^1H and ^{13}C spectra, respectively. All NMR pulse sequences were run using standard Varian 5.1 or JEOL Plexus 3.1 software. The LRCOSY experiment employed a delay time (Δ) of 300 ms before and after the mixing pulse.[19] The HMQC spectra were optimized for an average $^1J_{C,H}$ of 135 Hz; the HMBC spectra were optimized for $J_{C,H}$ of 4.5, and 7.0 Hz. Selective INEPT experiments were performed with excitation and refocusing delays optimized for $J_{C,H}$ = 7 Hz.[20] Difference NOE (DNOE) were recorded with 1024 accumulated transients each of the on-resonance (saturation) and off-resonance (negative) spectra acquired in repetitive blocks of 16 transients each. The irradiation delay was set to 8 s. No special precautions were taken in sample preparation prior to recording the DNOE spectra (no degassing, etc). Inverse gated decoupled carbon spectra were recorded for integration of carbon resonances. Infrared spectra were recorded on a Perkin-Elmer 1800 FTIR; UV spectra were recorded on a Hewlett-Packard 8452A; MS spectra were recorded on a Finnigan MAT 90 in either CI (ammonia, 140 eV) or EI (70 eV) mode as indicated; optical rotations were recorded on a Rudolph Research Autopol III polarimeter; melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Isolation of 1. The seeds of *Uvaria tonkinensis* were collected on Hainan Island (Hainan Dao), People's Republic of China; a voucher speciman is on deposit in the herbarium of the South China Institute of Botany, Chinese Academy of Sciences. The dried, pulverized seeds (1.2 kg) were extracted with 95% ethanol (3 X 2.5 L, rt) and following filtration the extract was evaporated to dryness in vacuo. The residue was fractionated on a silica gel column eluting with pet ether (bp 60 - 90 °C), pet ether:ethyl acetate (95:5), and then pet ether: ethyl acetate (80:20). From the fraction eluting with pet ether:ethyl acetate (95:5), colorless crystals of **1** precipitated and were collected by filtration. Recrystallization from pet ether (bp 60 - 90 °C) gave 46 mg of **1**.

Tonkinenin A[1]. Mp 158 - 159 °C; $[\alpha]_D^{24}$ -21.6 (*c* 1.71, MeOH); UV (MeOH) λ_{max} 232 nm (ε 46,900), 274 (2,600), 314 (1,200); IR (KBr) 3423 (OH), 1716 (C=O), 1703 (C=O), 1694 (C=O), 1272 (ArC(O)-O-C), 1113 (C-OH), 1098 (C-OH), 714 (CH=CH) cm^{-1}; ^1H and ^{13}C see Table 1; EIMS (70 eV) *m/z* relative intensity (%) 384 (36, $[M+2]^+$), 383 (78, $[M+1]^+$), 366 (60, $[M+2-H_2O]^+$), 365 (84, $[M+1-H_2O]^+$), 347 (4, $[M+1-2H_2O]^+$), 261 (58, see text), 260 (31), 243 (25, $[261 - H2O]^+$), 138 (32, see text), 123 (53, see text), 122 (59, see text), 106 (70), 105 (100, see text); HRMS (CI, ammonia, 140 eV) *m/z* 383.1147 calc'd for $C_{21}H_{19}O_7$ 383.1131.

Preparation of (R)- and (S)-O-Methylmandelate Esters 2 and 3. To a solution of **1** (8.2 mg, 0.021 mmol), dicyclohexylcarbodiimide (DCC, 12.8 mg, 0.042 mmol) and 4-N,N-dimethylaminopyridine (DMAP, 6.7 mg, 0.055 mmol) in anhydrous methylene chloride (2 mL) cooled to 0 °C was added a solution of (*R*)- or (*S*)-*O*-methylmandelic acid (3.8 mg, 0.023 mmol) also in anhydrous methylene chloride precooled to 0 °C. The reaction solution was stirred at 0 °C for 15 min, then the temperature was allowed to rise to room temperature

and the reaction solution stirred for an additional 45 min, at which time the TLC (SiO_2, CH_2Cl_2:MeOH, 100:3) indicated that all of **1** had reacted. The solvent was removed in vacuo and the residue purified by prep TLC (CH_2Cl_2:MeOH, 100:3) to give the (*R*)-*O*-methylmandelate ester **2** (9.9 mg, 90%), or the (*S*)-*O*-methylmandelate ester **3** (10.5 mg, 91%), respectively. **(*R*)-*O*-Methylmandelate Ester 2.** Mp 61 - 62 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (dd, *J* = 8.5, 1.2 Hz, 2H: H2"/6"), 7.82 (dd, *J* = 8.5, 1.2 Hz, 2H: H2'/6'), 7.54 (tt, *J* = 7.4, 1.2 Hz, H4"), 7.53 (tt, *J* = 7.3, 1.2 Hz, H4'), 7.41 (dd, *J* = 8.5, 7.3 Hz, 2H: H3"/5"), 7.35 (dd, *J* = 8.5, 7.3 Hz, 2H: H3'/5'), 7.25 (dd, *J* = 7.9, 1.8 Hz, 2H: $H4_m/8_m$), 7.06 (m, 3H: $H5_m/7_m$, $H6_m$), 6.83 (dd, *J* = 10.4, 3.0 Hz, H4), 6.25 (dd, *J* = 10.4, 1.8 Hz, H3), 5.85 (d, *J* = 5.5 Hz, H6), 5.71 (ddd, *J* = 5.5, 3.0, 1.8 Hz, H5), 4.75 (s, $H2_m$), 4.68 (d, J_{AB} = 11.0 Hz, $H7_{proR}$), 4.62 (d, J_{AB} = 11.0 Hz, $H7_{proS}$), 3.5 (bs, 1-OH)[21], 3.33 (s, OCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.7 (C2), 169.2 ($C1_m$), 165.9 (C7"), 164.9 (C7'), 143.9 (C4), 135.1 ($C3_m$), 133.6 (C4'), 133.4 (C4"), 129.8 (2C: C2'/6'), 129.7 (2C: C2"/6"), 129.1 (C1")[22], 128.7 ($C6_m$), 128.5 (7C: C3, C3'/5', C3"/5", $C5_m/7_m$)[23], 128.3 (C1')[22], 126.6 (2C: $C4_m/8_m$), 82.0 ($C2_m$), 75.8 (C1), 71.8 (C6), 68.5 (C5), 63.9 (C7), 57.4 (OCH_3); HRMS (CI, ammonia, 140 eV) *m/z* relative intensity (%) 548.1891 (100, $[M+1+NH_3]^+$) calc'd for $C_{30}H_{30}NO_9$ 548.1920. **(*S*)-*O*-Methylandelate Ester 3.** Mp 59 - 60 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (dd, *J* = 8.4, 1.2 Hz, 2H: H2"/6"), 7.89 (dd, *J* = 8.4, 1.2 Hz, 2H: H2'/6'), 7.65 (tt, *J* = 7.6, 1.2 Hz, H4"), 7.52 (tt, *J* = 7.6, 1.2 Hz, H4'), 7.39 (dd, *J* = 8.4, 7.6 Hz, 2H: H3'/5'), 7.38 (dd, *J* = 8.4, 7.6 Hz, 2H: H3"/5"), 7.29 (dd, *J* = 7.6, 2.0 Hz, 2H: $H4_m/8_m$), 7.24 (m, 3H: $H5_m/7_m$, $H6_m$), 6.95 (dd, *J* = 10.4, 2.4 Hz, H4), 6.28 (dd, *J* = 10.4, 1.2 Hz, H3), 5.96 (ddd, *J* = 5.6, 2.4, 1.2 Hz, H5), 5.83 (d, *J* = 5.6 Hz, H6), 4.74 (s, $H2_m$), 4.61 (d, J_{AB} = 10.8 Hz, $H7_{proR}$), 4.09 d, J_{AB} = 10.8 Hz, $H7_{proS}$), 3.29 (s, OCH_3), 3.1 (bs, 1-OH).[21] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.5 (C2), 169.1 ($C1_m$), 165.4 (C7"), 165.2 (C7'), 143.4 (C4), 135.4 ($C3_m$), 133.8 (C4"), 133.3 (C4'), 129.9 (2C: C2"/6"), 129.7 (2C: C2'/6'), 129.2 ($C6_m$), 129.1 (C1')[22], 128.74 (4C: C3'/5', $C5_m/7_m$); 128.69 (C1")[22], 128.6 (C3), 128.4 (2C: C3"/5"), 127.0 (2C: $C4_m/8_m$), 82.3 ($C2_m$), 76.0 (C1), 71.9 (C6), 68.7 (C5), 63.6 (C7), 57.4 (OCH_3). HRMS (CI, ammonia, 140 eV) *m/z* relative intensity (%) 548.1918 (100, $[M+1+NH_3]^+$) calc'd for $C_{30}H_{30}NO_9$ 548.1920.

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23 Resonances overlapped giving rise to only two poorly resolved signals which together integrated to seven carbons in an inverse gated decoupled experiment: δ 128.50 and 128.47.

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