Application of the Anionic Oxy-Cope Rearrangement to Stereocontrolled Synthesis of the A/B Subunit of Cytotoxic 8,9-Seco-ent-kaurenes

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Received 21 August 1991

Methodology is described for expedient synthesis of the A/B framework of 8,9-seco-ent-kaurenes and for introduction of the 5-methylene-2-cyclopentenone moiety. In the first part of the study, a sequence of only six steps is necessary to convert 2-(hydroxymethylene)cyclohexanone to a key functionalized intermediate. Five of the transformations are 100% stereocontrolled as a direct result of complementary steric biases that operate in the desired direction. The final target is arrived at by selective protection/oxidation of the oxygenated centers. This first synthetic entry to the structural core of the titled diterpenes is expected to guide the future de novo acquisition of these cytotoxic agents.

Intensive investigation by several Japanese research groups of plants from the genus 
Rabdosia (Labiatae) has resulted in the isolation and identification of seven 8,9-seco-ent-kaurene diterpenes.1-7 These include shikodemedin (1a), rabdalatilolin (1b), shikocin (1c), O-methylshikocin (1d), shikokiamedin (2a), epoxysikocin (2b), and O-methylepoxysikocin (2c). Subsequent screening for cytotoxic activity has shown 1a to be a potent inhibitor of cultured FM 3A/B rat mammary cancer cells.8 The other members of this class exhibit the same antitumor response, although to a lesser degree. As a result of its scarcity, 1a has not been developed as an agent that might contribute to our understanding of leukemia and other types of cancer at the molecular level.

The structural features of shikodemedin and its congeners, which were originally elucidated by X-ray diffraction, are sufficiently unusual that they have commanded interest in these laboratories9 and elsewhere.10 Of particular note is the intracyclic bridgehead double bond that forms part of a 5-methylene-2-cyclopentenone unit in 1. Central to our development of a synthetic route to this class of compounds was the realization that the bicyclo[7.2.1]dodec-1(12)ene-6,11-dione core 3 of rings A and B is related to spirocycle 5 via an oxy-Cope rearrangement that would lead initially to 4.

Accordingly, the present goals were to gain access to the protected aldol 6 in a fully stereocontrolled manner and to transform this intermediate into 3. The possibility of preparing 1a by a related protocol (viz 7 → 8) would thereby be accorded reasonable precedence.

Results and Discussion

The extent to which the aliphatic Claisen rearrangement can be relied upon to control stereoselectivity11 prompted its utilization at the outset. For the sake of completeness, 2-(hydroxymethylene)cyclohexanone was condensed12 with both isomers of 3-(trimethylsilyl)-2-propen-1-ol (Schemes 1 and 2). Although Z-alcohol 10 had been earlier produced by semihydrogenation of the corresponding alkyne,13 we chose to utilize a two-step procedure involving hydroboration with diborylbenzene followed by protonolysis with acetic acid so as to skirt possible overreduction. The pure E isomer 15 was prepared by dilithiation of propargyl alcohol, silylation with Me3SiCl, and Red-Al reduction of the hyrolysis product according to precedent.14

Once the enol ethers 11 and 16 were available, they were independently heated in decalin or undecane at 175°C for 18-20 hours. The Z isomer 11 isomerized smoothly to afford 14 exclusively (Scheme 1). Thus, the [3,3] sigmatropic shift in this case proceeds strictly via chair transition state 13. The steric congestion present in boat conformation 12 is particularly adverse to its involvement on a competitive basis. This is not so for 16 where chair option 18 is now more crowded than the boat alternative 17. These steric control elements act to force approximately 25% of the aldehydeic product to be formed via 17. For the present purposes, it is particularly relevant that the olefinic geometry localized in the double bonds of 11 is transformed into two unequivocally defined stereogenic centers in 14.
While aldehydes 14 and 19 can easily be distinguished by means of their respective -CHO singlets ($\delta = 9.48$ and 9.23 in CDCl$_3$), their relative configurations at this stage were deduced solely on the basis of mechanistic reasoning. The correctness of these assignments and the strategic importance of the clean conversion to 11 and 14 shall become very apparent in the sequel.

Of the catalysts examined for promoting intramolecular 5-exo,trans cyclization within 14 and 19, ethylaluminum dichloride emerged as the most efficacious. Both reactions were fully stereocontrolled, with 14 giving rise cleanly to anti aldol 20a and 19 leading to syn diastereomer 23a (Scheme 3). These sensitive $\beta$-hydroxy ketones were silylated prior to further handling.

The excellent stereoselectivity associated with these ring closure reactions is indicative that several stereochemical determinants are operating in the same direction. The need to position the terminal carbon of the allylsilane moiety in close proximity to the aldehyde center limits 14 to conformations such as those depicted by Newman projections A–C.
For 19, the corresponding structural alignments are D–F. Once Lewis acid complexation occurs at oxygen from that direction anti to the R group of the aldehyde,16 two product-related steric biases gain importance. The first involves those nonbonded interactions operating between the collective substituents. Thus, A and B are clearly more sterically congested than C; likewise, the spatial disposition of the groups in E and F are more encumbered than that present in D. Facial selectivity associated with bonding to the carbonyl carbon must also be considered. In both C and D, the bulky cationic oxygen center is oriented in the direction of a hydrogen atom rather than toward vinyl. Therefore, the combined energetic advantages enjoyed by these rotamers are responsible for their involvement of the antiperiplanar transition states of choice for clean conversion to 20a and 23a, respectively.

Proper distinction between 20b and 23b could now be made on the basis of chemical reactivity. Thus, 20b condensed smoothly with vinylicerium dichloride,17 while 23b was totally unreactive. The syn orientation of the OTBDMS group so blockades the ketone functionality in 23b that condensation reactions with organometallic reagents are kinetically deterred.

The complete stereocontrol achieved in the formation of 21 likely stems from the fact that the β-siloxy substituted carbon is projected equatorially such that axial attack is favored. Unfortunately, we were unable to corroborate the relative configurations of 21 by NOE studies at 500 MHz.

With arrival at 21, the stage was set for the pivotal [3,3] sigmatropic rearrangement. However, attempts to capitalize on the kinetic acceleration associated with the anionic oxy-Cope reaction proved disappointing. Exposure of 21 to KH, KN(SiMe3)2, and other potassium bases with or without added 18-crown-6 resulted in no reaction at room temperature; when heated, rapid conversion to a black tarry material took place. This turn of events was ultimately traced to the sensitivity of the anticipated ketonic product to strong bases. As a result, this complication could easily be skirted by simply heating 21 in decalin at 190 °C for 9 h. These purely thermal conditions provided for the efficient formation of 22 (92%).

As shown in Scheme 4, the lability of 22 under strongly alkaline conditions could be skirted to achieve its conversion to 28. Initially, a second carbonyl group was directly introduced to provide 24. This macrocyclic diketone proved to be a more sensitive compound than expected, being prone to decomposition simply on standing in neat condition at room temperature. Our apprehensiveness regarding a comparable level of instability of 28 proved, however, to be unfounded.

Several routes from 22 to 28 were briefly examined. The illustrated sequence was determined to be serviceable, although the yields of the individual steps have not been maximized. A number of points are noteworthy. The DIBAL-H reduction of 22 proved to be 100% stereose-
lective. Product stereochemistry has been arbitrarily assigned. Since the final step was to involve reoxidation of this center, more definitive stereochemical proof was not sought. The virtually complete stereocontrol achieved in the methylation and selenylation of enolates derived from 26 conforms to expectations associated with kinetically favored exo capture of electrophiles by related bicyclic systems. Trigonalization of the α-carbonyl site was realized by exposure of 27b to the chromium trioxide-dipyridine complex. Under these conditions, selenoxide elimination and oxidation to the ketone were accomplished concurrently. Dienone 28 exhibited spectral properties fully commensurate with its structural assignment.

In summary, this study describes successful application of the oxy-Cope rearrangement to the synthesis of 10-methylbenzocyclo[7,2.1]dodec-11(12)-ene-6,11-dione (28), an appropriately functionalized model for the A/B ring system of the 8,9-seco-ετ-kaurene diterpenes. The process that regulates access to 22 involves six steps, five of which are fully stereocontrolled. Only the protective silylation maneuver falls outside of this boundary claim. On the practical side, this sequence leading directly to the structural core is impressively short. As this strategy applies to ultimate arrival at shikomedin, proper allowance has been made for those operations required to develop the 5-methylene-2-cyclopentenone part structure. Further synthetic studies involving those tricyclic intermediates necessary to achieve this objective will be reported in due course.

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. 1H NMR spectra were recorded at 300 or 250 MHz and the 13C NMR data obtained at 75 or 20 MHz as iodide. Mass spectra were measured on a Kratos MS-30 instrument at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All flash chromatographic separations were carried out on Merck silica gel 60 (200–240 mesh) and reactions were routinely performed under an inert atmosphere (nitrogen or argon) unless otherwise indicated. Solvents were reagent grade and dried prior to use.

2-(E)-(Z)-3-(Trimethylsilyl)allyloxy)methylene)cyclohexanone (11): A solution of 2-(hydroxymethylene)cyclohexanone (12.0 g, 95 mmol) in dry benzene (350 mL) was treated with 103 (14.0 g, 108 mmol) and TsOH (350 mg) and heated at reflux under a Dean–Stark trap for 10 h. The cooled mixture was concentrated, filtered through a column of silica gel (elution with 1:1 petroleum ether/EtOAc), and evaporated. Chromatography (elution with 95:5 petroleum ether/EtOAc) followed by Kugelrohr distillation (160°C/0.3 Torr) gave 11 (13.7 g, 61%) as a faint yellow oil.

IR (neat): ν = 1670 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.30 (s, J = 2.0 Hz, 1H), 6.32 (m, 1H), 5.80 (dd, J = 14.5, 1.3 Hz, 1H), 4.49 (dd, J = 6.5, 1.3 Hz, 2H), 2.38 (td, J = 6.4, 2.0 Hz, 2H), 2.28 (t, J = 6.6 Hz, 2H), 1.70 (m, 4H), 0.99 (s, 9H).

13C NMR (75 MHz, CDCl₃): δ = 200.1, 155.3, 141.2, 135.3, 115.7, 73.6, 39.4, 23.1, 22.9, 22.6, −0.18.

MS: m/z (M⁺ − Me₂S) 133.0973; found 133.1033.

(4R,5R*)-2-Oxo-1-[(R*)-1-(trimethylsilyl)allyl]cyclohexanecarboxaldehyde (14): A solution of 11 (3.1 g, 13 mmol) in anhyd. decalin (100 mL) was heated at 175°C under an argon atmosphere for 20 h, cooled to r.t., and poured onto a column of silica gel. The decalin was removed by elution with petroleum ether. An increase in polarity to 96:4 petroleum ether/EtOAc afforded 14 (2.1 g, 68%) as a colorless crystalline solid; mp 49°C.

IR (KBr) ν = 1710, 1690 cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 9.48 (s, 1H), 5.65 (m, 1H), 4.90 (m, 2H), 2.6–1.5 (series of m, 8H), 0.04 (m, 10H).

13C NMR (20 MHz): δ = 210.0, 201.2, 135.5, 115.8, 66.5, 41.2, 39.4, 33.0, 26.4, 21.4, −0.36.

MS: m/z (M⁺) 238.1389, found 238.1366.


2-(E)-(E)-(Z)-3-(Trimethylsilyl)allyloxy)methylene)cyclohexanone (16): A solution of 2-(hydroxymethylene)cyclohexanone (1.0 g, 7.9 mmol) in dry benzene (20 mL) was added 15 (1.4 g, 1.1 mmol) and TsOH (30 mg). This mixture was refluxed for 6 h under a Dean–Stark trap while being blanketed with argon. The predescribed workup afforded 1.1 g (58%) of 16 as a pale yellow oil.

IR (neat): ν = 1670 cm⁻¹.

IR (neat): ν = 1720, 1680 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.34 (s, 1H), 6.1–5.9 (m, 2H), 4.5 (d, J = 4.4 Hz, 2H), 2.47 (t, J = 6.5 Hz, 2H), 2.35 (t, J = 6.4 Hz, 3H), 1.9–1.6 (m, 4H), 0.08 (s, 9H).

13C NMR (75 MHz, CDCl₃): δ = 220.0, 177.9, 163.1, 155.5, 138.1, 98.7, 62.3, 46.2, 45.8, 45.3, 21.0.

MS: m/z (M⁺ − Me₂S) 133.0973, found 133.1025.

(2R,5R*)-2-Oxo-1-[(S*)-1-(trimethylsilyl)allyl]cyclohexanecarboxaldehyde (19): Heating a 1.0 g (4.2 mmol) sample of 16 in dry undecane (20 mL) at 175°C under argon for 18 h and workup as before gave 600 mg (60%) of a 3:1 mixture of 19 and 14.

For 19:

IR (neat): ν = 1670, 1680 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 9.23 (s, 1H), 6.0–5.45 (m, 1H), 5.0–4.8 (m, 2H), 2.6–1.6 (series of m, 9H), 0.0–0.01 (m, 9H).

13C NMR (75 MHz, CDCl₃): δ = 208.0, 203.0, 134.1, 116.1, 67.5, 41.4, 38.6, 30.3, 25.3, 21.7, −0.3, −0.6, −1.5.

MS: m/z (M⁺ − CO) 210.1440, found 210.1407.

(4R,5R*)-4-(tert-Butylidimethylsilyloxy)pirro|d|4,5)-1-dec-1-en-6-one (20b):

IR (neat): ν = 1695 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 5.75–5.65 (m, 2H), 4.49 (dd, J = 2.6, 5.8 Hz, 1H), 2.7–1.55 (series of m, 10H), 0.83 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H).
\[ \text{Synthesis} \]

13C NMR (75 MHz, CDCl\(_3\)): \( \delta = 210.7, 134.4, 128.3, 78.1, 67.2, 42.1, 41.8, 38.6, 27.0, 25.7, 22.5, 17.8, -3.8, -4.8. \]

MS: m/z (M\(^+\)) calcd 280.1858, found 280.1836.

**Anal.** Caled for C\(_{14}\)H\(_{24}\)O\(_{4}\)Si: C, 68.52; H, 10.06. Found: C, 68.46; H, 10.01.

\((\pm)-(4R,5S,5S*)-4-(tert-Butyldimethylsiloxyl)-6-vinylspiro[4.5]-
\text{dec-1-en-6-one (21)}\):

A cold (\(-78^\circ\text{C}\), magnetically stirred slurry of anhydride CeCl\(_3\) (4.0 g, 16.3 mmol) in dry THF (150 mL) was treated with vinylmagnesium bromide (18 mL of 1.0 M in THF, 10 mmol) and the mixture was stirred at this temperature for 30 min. A solution of 20b (3.9 g, 13.9 mmol) in dry THF (50 mL) was quickly introduced and the mixture was allowed to warm to r.t. After 30 min, the mixture was returned to \(-78^\circ\text{C}\) for a second addition of the Grignard reagent (10 mL). After a return to r.t. and 30 min of added stirring, the NH\(_4\)Cl solution (5 mL) was introduced and the mixture was poured into water (150 mL). The aqueous phase was extracted with EtOAc (3 x 400 mL) and the combined organic layers were washed with brine (200 mL), dried (MgSO\(_4\)), filtered, and evaporated. Chromatography of the residue (2% EtOAc in petroleum ether) afforded 3.2 g (75%) of 21 as a colorless oil.

IR (neat): \(\nu = 3465 \text{ cm}^{-1}\).

**1H** NMR (300 MHz, CDCl\(_3\)): \( \delta = 6.21 \text{ (dd, } J = 10.8, 17.2 \text{ Hz, 1H}), 5.88 \text{ (td, } J = 6.5, 1.9 \text{ Hz, 1H}), 5.73 \text{ (td, } J = 6.5, 2.4 \text{ Hz, 1H}), 5.30 \text{ (dd, } J = 17.2, 1.0 \text{ Hz, 1H}), 4.95 \text{ (dd, } J = 10.7, 2.0 \text{ Hz, 1H}), 4.88 \text{ (s, 1H)}, 4.03 \text{ (s, } J = 8.4 \text{ Hz, 1H}), 2.5-1.0 \text{ (series of m, 10H)}, 0.93 \text{ (s, 9H)}, 0.12 \text{ (s, 3H)}, 0.07 \text{ (s, 3H)}.

**13C** NMR (75 MHz, CDCl\(_3\)): \( \delta = 144.3, 134.1, 129.2, 111.5, 85.4, 76.0, 54.9, 40.8, 35.5, 34.1, 25.8, 22.6, 20.7, 17.8, -4.5, -5.3. \)

MS: m/z (M\(^+\)) calcd 308.2172, found 308.2152.

**Anal.** Caled for C\(_{14}\)H\(_{24}\)O\(_{4}\)Si: C, 70.07; H, 10.46. Found: C, 69.86; H, 10.47.

\((\pm)-(1R,10R*)-10-(tert-Butyldimethylsiloxyl)bicyclo[7.2.1].1-dodec-9(12)-ene-4-one (22)\):

A solution of 21 (62 mg, 0.2 mmol) in dry decalin (6 mL) was heated at gentle reflux under argon for 9 h. The cooled mixture was poured onto a column of silica gel and flushed with petroleum ether to remove the decalin. Subsequent elution with 5% EtOAc in petroleum ether gave pure 22 (57 mg, 92%) as a white solid; mp 66-67°C.

IR (CHCl\(_3\)): \(\nu = 1670 \text{ cm}^{-1}\).

**1H** NMR (300 MHz, CDCl\(_3\)): \( \delta = 5.17 \text{ (s, 1H), 4.63 \text{ (d, } J = 8.6 \text{ Hz, 1H), 3.29 \text{ (dd, } J = 16.5, 11.3 \text{ Hz, 1H}), 2.8-1.1 \text{ (series of m, 14H)}, 0.96 \text{ (s, 9H), 0.12 \text{ (s, 6H)}.

**13C** NMR (75 MHz, CDCl\(_3\)): \( \delta = 215.3, 143.3, 135.0, 78.9, 42.3, 42.1, 37.9, 37.4, 33.6, 25.9, 25.6, 24.7, 22.1, 18.0, -4.5, -4.9. \)

MS: m/z (M\(^+\)) calcd 308.2172, found 308.2169.

**Anal.** Caled for C\(_{14}\)H\(_{24}\)O\(_{4}\)Si: C, 70.07; H, 10.46. Found: C, 70.01; H, 10.49.

\((\pm)-(4R,5S*,5S*)-4-(tert-Butyldimethylsiloxyl)spiro[4.5]-
\text{dec-1-en-6-one (23b)}\):

\((\pm)-(4R,5S*,5S*)-4-HydroxySpiro[4.5]-
\text{dec-1-en-6-one (23a)}\):

A solution of 19 (800 mg, 3.36 mmol) in CH\(_2\)Cl\(_2\) (25 mL) was cooled to \(-78^\circ\text{C}\) under argon, treated with Et\(_2\)AlCl\(_3\) (13.4 mL of 1 M in hexanes, 0.13 mmol), and stirred at this temperature for 1 h. Workup in the manner predescribed for 20a furnished 410 mg (4%) of 23a, which was immediately silylated.

\((\pm)-(4R,5S*,5S*)-4-(tert-Butyldimethylsiloxyl)spiro[4.5]-
\text{dec-1-en-6-one (23b)}\):

The above material 23a (400 mg) was dissolved in cold (0°C) CH\(_2\)Cl\(_2\) (12 mL) and treated sequentially with 2,6-lutidine (0.60 mL, 4.8 mmol) and tert-butyldimethylsilyle tri fluoride (0.69 mL, 2.9 mmol). After 15 min of stirring at 0°C, the usual workup followed to give 484 mg (72%) of 23b as a colorless oil.

IR (neat): \(\nu = 1695 \text{ cm}^{-1}\).

**1H** NMR (300 MHz, CDCl\(_3\)): \( \delta = 5.70-5.30 \text{ (m, 2H), 4.84 \text{ (dd, } J = 5.0, 6.3 \text{ Hz, 1H), 2.67-1.61 \text{ (series of m, 10H)}, 0.88 \text{ (s, 9H), 0.07 \text{ (s, 3H)}, 0.06 \text{ (s, 3H)}, \).
A solution of 25b (1.44 g, 3.62 mmol) in dry THF (100 mL) was treated with a solution of Bu$_3$NF in THF (15 mL of 1 M) and heated at 55°C for 10 h. Following solvent evaporation, the residue was chromatographed (elution with 30% EtOAc in petroleum ether) to give 990 mg (96 %) of 25c as a colorless oil.

IR (neat): ν = 3600–3300 cm$^{-1}$.

$^{1}$H NMR (300 MHz, CDCl$_3$): δ = 5.36 (s, 1 H), 4.8–4.6 (m, 3 H), 3.95–3.50 (m, 5 H), 3.39 (s, 3 H), 3.0–2.65 (m, 1 H), 2.3 (m, 1 H), 2.3 (m, 1 H), 2.1 (m, 1 H), 2.0–1.2 (series of m, 12 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ = 142.5, 130.4, 93.9, 79.4, 73.1, 71.7, 76.0, 58.9, 41.0, 39.9, 35.5, 29.4, 29.3, 29.1, 26.8, 22.0.

MS: m/z (M$^+$) caled 284.1897, found 284.1927.

A solution of 26a (156 mg, 1.56 mmol) in CH$_2$Cl$_2$ (3 mL) was treated with pyridine (0.25 mL, 3.13 mmol). After 30 min, 25e (74 mg, 0.26 mol) dissolved in CH$_2$Cl$_2$ (1 mL) was introduced and the mixture was rapidly stirred for 15 min prior to filtration over silica gel (EtO$_2$Eulution) to remove the chromium salts. After evaporation, the residue was chromatographed (elution with 30% EtOAc in petroleum ether) to give 26a (62 mg, 85 %) as a colorless oil.

IR (neat): ν = 1685 cm$^{-1}$.

$^{1}$H NMR (300 MHz, CDCl$_3$): δ = 7.22 (s, 1 H), 4.7–4.5 (m, 2 H), 3.70–3.45 (m, 4 H), 3.34 (s, 3 H), 3.2–3.0 (m, 2 H), 2.60–2.45 (m, 2 H), 2.30 (d, J = 8.8 Hz, 1 H), 2.05–1.60 (m, 5 H), 1.5–1.0 (m, 6 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ = 209.8, 162.0, 143.4, 93.8, 74.0, 71.7, 66.9, 58.9, 42.0, 36.1, 34.4, 26.9, 25.6, 24.8, 24.1, 22.0.

MS: m/z (M$^+$) caled 282.1831, found 282.1856.

Anal. Caled for C$_{15}$H$_{16}$O$_2$: C, 68.05; H, 9.28. Found: C, 68.11; H, 9.32.

A solution of 26a (72 mg, 0.096 mmol) in dry THF (2 mL) was treated at –78°C with a solution of potassium hexamethyldisilazide (0.23 mL of 0.5 M in hexanes, 0.11 mmol) and stirred at this temperature for 30 min. A solution of PhSeCl (21 mg, 0.11 mmol) in THF (0.5 mL) was quickly introduced and stirring at –78°C was maintained for an additional 30 min. Sat. NH$_4$Cl (5 drops) was added, the mixture was allowed to warm to r.t., at which point it was poured into water (10 mL) and extracted with CHCl$_3$ (3×15 mL). The usual workup (see above) provided 26b (44 mg) as a yellow oil.

$^{1}$H NMR (300 MHz, CDCl$_3$): δ = 7.85 (m, 2 H), 7.3 (m, 4 H), 4.73 (dd, J = 13.5, 6.9 Hz, 2 H), 3.75–3.50 (m, 4 H), 3.37 (s, 3 H), 3.35 (m, 1 H), 3.0 (m, 1 H), 2.6–0.3 (series of m, 12 H), 1.38 (s, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ = 201.2, 159.9, 139.7, 137.7, 128.6, 128.7, 117.1, 94.3, 75.5, 71.8, 66.9, 59.0, 57.1, 51.4, 33.7, 30.0, 25.3, 24.6, 24.4, 24.0, 22.0.

MS: m/z (M$^+$) caled 452.1465, found 452.1453.

We thank the National Institutes of Health for support of this research through Grant CA-12115.


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We thank the National Institutes of Health for support of this research through Grant CA-12115.
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