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Chemoenzymatic Formal Total Synthesis of Pancratistatin from Narciclasine-Type Compounds via Myers Transposition: Model Study for a Short Conversion of Narciclasine to Pancratistatin

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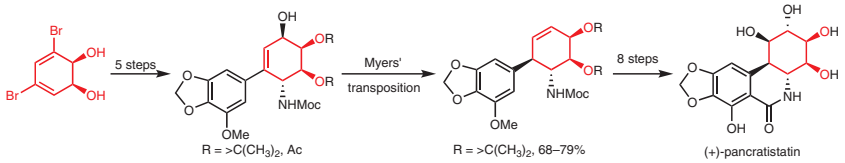
Dedicated to Professor Victor Snieckus on the occasion of his 80th birthday and in recognition of his many contributions to the art of organic synthesis



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Abstract A formal total synthesis of pancratistatin was accomplished by conversion of advanced intermediates, used in the synthesis of narciclasine, to pancratistatin precursors via Myers' reductive transposition as the key strategic step. The synthesis began with the whole cell fermentation of *m*-dibromobenzene with JM109(pDTG601a), a recombinant strain that over-expresses toluene dioxygenase, which provided the corresponding *cis*-dihydrodiol **16** as a single isomer with complete optical purity. The key reductive transposition of the allylic alcohol **8a** to olefin **9a** allowed for further installation of the C-1/C-2 *trans*-diol, required for the pancratistatin scaffold, through the introduction of a cyclic sulfate and its subsequent opening. The formal synthesis of pancratistatin was accomplished in 14 steps (12 operations) from commercially available *m*-dibromobenzene. Experimental and spectral data are provided for all new compounds.

Key words narciclasine, pancratistatin, toluene dioxygenase, enzymatic dihydroxylation of arenes, reductive transposition of allylic alcohols

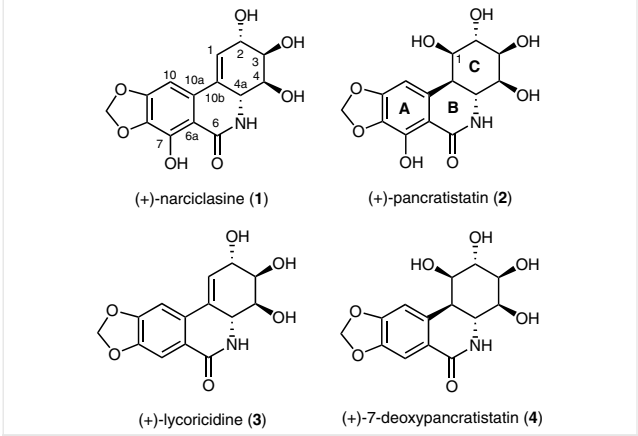
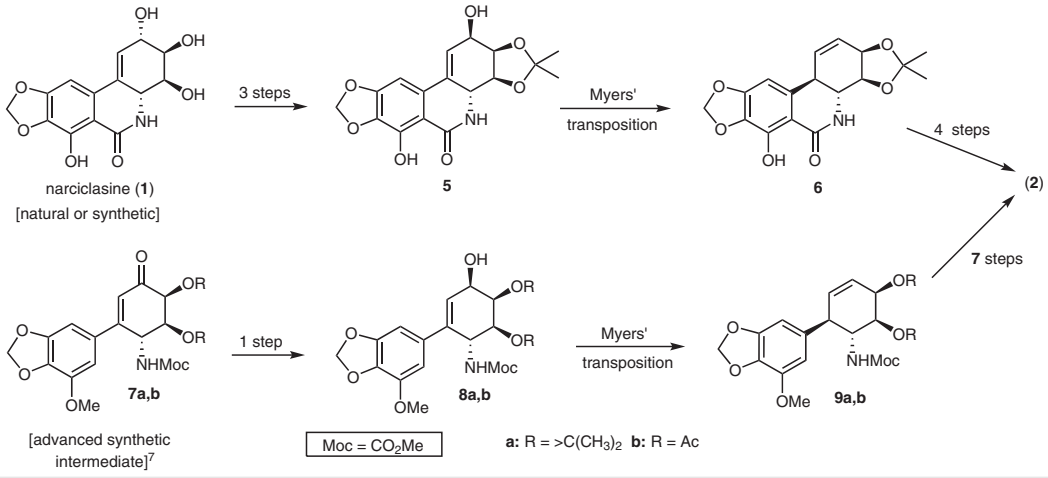


Figure 1 Representative Amaryllidaceae constituents

The highly bioactive Amaryllidaceae constituents (+)-narciclasine (**1**), (+)-pancratistatin (**2**) and their congeners, shown in Figure 1, have been the focus of intense investigations for many years. Their biological activity is unique as these compounds induce apoptosis at very low concentrations, targeting the tumor cells selectively.[1] More advanced evaluations, such as target identification, pharmacokinetics and animal studies, are hampered by limited availability of these compounds from natural sources. Pancratistatin is isolated at levels of ca 19 mg/kg[2] while narciclasine is available at higher levels of 30–140 mg/kg.[3] It is this lack of availability that has led to many attempts at providing these compounds by total synthesis and, indeed, many creative approaches to these compounds, as well as to their unnatural derivatives, have been published.[4,5]

In 2001, Pettit reported a ten-step conversion of the more abundant narciclasine to pancratistatin.[5h] Around that time we published a twelve-step (nine-operations) total synthesis of narciclasine that may be amenable to eventual optimization and scale up.[6,7] Commercially, narciclasine is available at a cost of $100–160/mg, most probably through isolation from daffodil bulbs.[8] Given these constraints in availability, we decided to investigate two distinct options: a) *de novo* synthesis of pancratistatin from intermediates that were utilized early on in our narciclasine synthesis and b) conversion of natural or synthetic narciclasine into pancratistatin. Both approaches rely on the Myers' reductive transposition of allylic alcohols[9] and the resulting *trans*-dihydroxylation of the ring-C olefin. In this paper, we report the successful preparation of the title natural product.



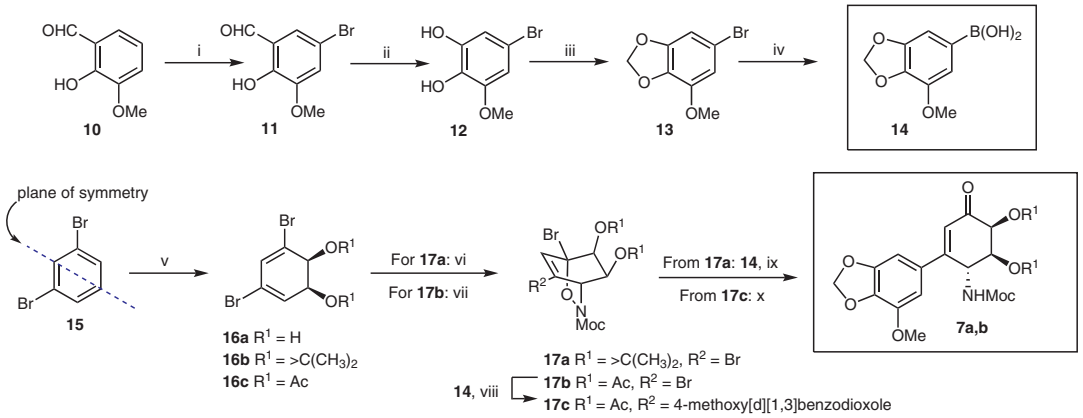
Scheme 1 Approaches to pancratistatin via Myers' reductive transposition

The two approaches to pancratistatin are shown in Scheme 1. In the first, we would assume the availability of either natural or synthetic narciclasine, which would be converted to alcohol **5** in three steps (protection, oxidation, reduction). Myers' reductive transposition of **5** with *o*-nitrobenzenesulfonylhydrazine (NBSH)[9] would furnish olefin **6** convertible to pancratistatin by *trans*-dihydroxylation and deprotection.

The second approach relies on the use of allylic alcohol **8a** or **8b**, either of which is produced by 1,2-reduction of the intermediate enone **7a** or **7b**. The acetonide **7a** was used previously in our synthesis of narciclasine.[7] The diacetate **7b** was prepared in order to avoid aromatization during the eventual closure of the phenanthridone ring B. If **7a** is used then acetonide/acetate exchange has to take place (the Banwell protocol[10] for the conversion of the carbamate to the isocyanate requires the use of triflic anhydride).

We have performed the nitroso-Diels–Alder reaction on the diacetate derived from diol **16a** and converted it to **17b** (Scheme 2). This maneuver reduces the number of steps in our previous synthesis of narciclasine from twelve to ten steps.[7] To confirm the stereochemical outcome of the cycloaddition, the acetates in **17b** were hydrolyzed and the resulting diol was converted to acetonide **17a**. In both cases the oxazines were obtained with identical regio- and stereoselectivity in the [4+2] cycloaddition.

Alcohol **8a**,**b** provides olefin **9a**,**b** via Myers' transposition and can be converted further to pancratistatin by known transformations (*trans*-dihydroxylation, Banwell's modification of the Bischler–Napieralski reaction,[10] and

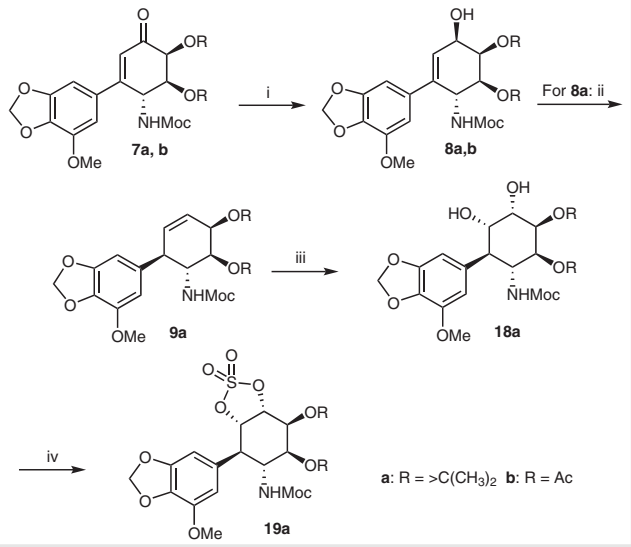


Scheme 2 Synthesis of the key intermediates, enones **7a**,**b**. *Reagents and conditions*: (i) Br_2, AcOH, NaOAc (90–95%, crude); (ii) H_2O_2 (30%), NaOH (2%), then HCl (2 M) (60–75%); (iii) CH_2I_2, K_2CO_3, DMF (59–78%); (iv) *t*-BuLi, THF, then $B(OMe)_3$ (crude boronic acid **14** is used in Suzuki coupling, isolated: 68–88%); (v) toluene dioxygenase in E.coli JM109(pDTG601A) (0.5–0.8 g/L); (vi) DMP, TsOH, then MocNHOH, $NaIO_4$, MeOH, H_2O (45–70%); (vii) Ac_2O, pyridine, CH_2Cl_2, then MocNHOH, $NaIO_4$, MeOH, H_2O (60–68%); (viii) $Pd(PPh_3)_4$, KF, benzene, H_2O, EtOH (51–86%); (ix) $Pd(PPh_3)_4$, Na_2CO_3, benzene, H_2O, EtOH, then $Mo(CO)_6$, MeCN, H_2O (60–72%); (x) $Mo(CO)_6$, MeCN, H_2O (50–80%).

deprotection). Because of the limited availability of natural or synthetic narciclasine, we chose to pursue the latter alternative first as a proof of principle study.

The synthesis of **7a**,**b** was accomplished by repetition and modest optimization of our published protocol[6] and is shown in an abbreviated form in Scheme 2. Bromide **13** is commercially available, but can also be prepared by known chemistry from *o*-vanillin, as described in our papers[6,7] and shown in Scheme 2. Oxazine **17a** (R^2 = Br) was subjected to Suzuki coupling with **14** and converted to **7a** directly without isolation of the intermediate. Oxazine **17b** (R^1 = Ac) was first converted to **17c** by Suzuki coupling and then subjected to the reduction with $Mo(CO)_6$ to yield **7b** (Scheme 2).

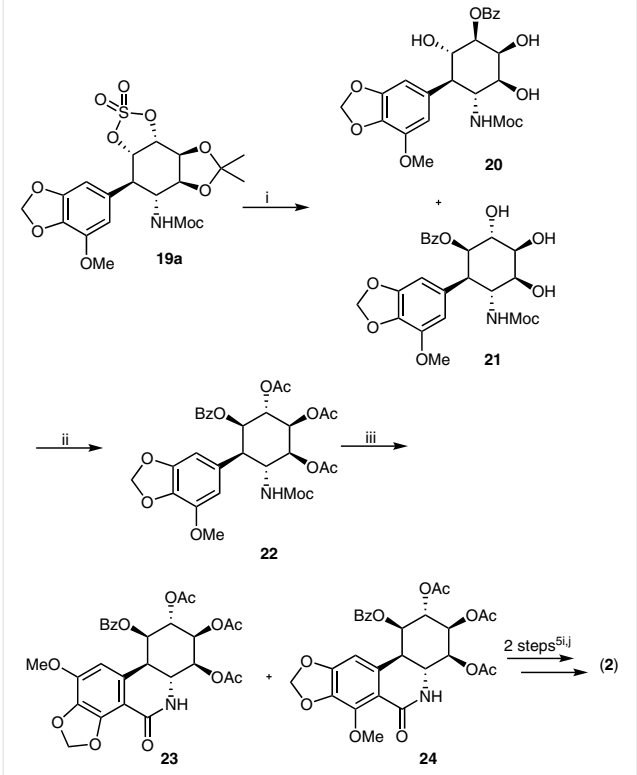
Luche reduction of enone **7a** produced allylic alcohol **8a** (Scheme 3). The use of the original procedure for Myers' reductive transposition led to a mixture of products that were difficult to separate and the protocol had to be modified. Following the report by Movassaghi, *o*-nitrobenzenesulfonylhydrazide (NBSH) was condensed with acetone to yield 2-nitro-N′-(propan-2-ylidene)benzenesulfonohydrazide (IP-NBSH), which is more stable and allows for greater variations in temperature, solvent, order of addition, and dilution of reagents.[11] Different azodicarboxylate and phosphine sources were screened and the use of di-*tert*-butyl azodicarboxylate (DBAD) together with triphenylphosphine gave the best results, with 68–79% yield of olefin **9a**.



Scheme 3 Synthesis of cyclic sulfate **19a**. *Reagents and conditions*: (i) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH (a: 68–90%, b: 62–87%); (ii) DBAD, IP-NBSH, PPh_3, THF, then CF_3CH_2OH, H_2O (a: 68–79%); (iii) OsO_4, NMO, acetone, H_2O (a: 50–61%); (iv) NaH, SDI, THF (a: 58–81%).

All attempts to accomplish the required *trans*-dihydroxylation through previously established methods of epoxide formation proved to be unsuccessful. Recent reports of the synthesis of Amaryllidaceae constituents by Kim's[5j] and McNulty's[12] groups describe similar difficulties in epoxidation of ring C in intermediates containing an electron-rich 7-methoxy-8,9-[1,3]-benzodioxole moiety of ring A. The use of classical procedures for epoxidation (bromohydrin, Sharpless or Shi-type epoxidations) led to decomposition or recovery of starting material. Only the use of *m*-CPBA led to the formation of the desired epoxide in moderate yield in McNulty's study,[12] while in our case these conditions did not lead to the desired epoxide. Such problems were not encountered in the epoxidations of ring C olefins in compounds lacking the C-7 hydroxyl or methoxy groups or with ring A containing additional electron-withdrawing groups.[5b,7] To overcome this obstacle, alternative route through a cyclic sulfate was chosen. Olefin **9a** was converted to the *cis*-diol **18a** by Upjohn dihydroxylation with OsO_4. [Conversion of **8b** to **9b** was problematic presumably because of acyl migration(s) to β-C-2 alcohol. This problem is not encountered in the synthesis of narciclasine where the α-C-2 alcohol is a benzoate.] The cyclic sulfate **19a** was synthesized in one step using safer and easier to handle 1,1′-sulfonyldiimidazole (SDI) than the more commonly used thionyl chloride or sulfuryl chloride (the use of the former reagent requires an additional oxidation step).

Nucleophilic opening of the cyclic sulfate **19a** with ammonium benzoate resulted in a mixture of esters **20** and **21**, with the preferential *trans*-diaxial attack at the desired C-1 position (**20**:**21**, 1:8.5; Scheme 4). Compound **21**, resulting



Scheme 4 Synthesis of triacetate **24**. *Reagents and conditions*: (i) $PhCO_2NH_4$, DMF, then H_2SO_4, H_2O, THF (**20**: 8%, **21**: 73%); (ii) Ac_2O, DMAP, Et_3N, CH_2Cl_2 (80%); (iii) Tf_2O, DMAP, CH_2Cl_2 (42–61%).

from the acid-catalyzed deprotection of the acetonide during workup, was protected as triacetate **22**, which underwent Banwell modified Bischler–Napieralski closure to the known phenanthridone **23** and its regioisomer **24** in the ratio of 1:9, respectively, as compared to the 1:7 ratio reported by Magnus[5e,f] and Kim.[5j] Compound **24** is converted to **2** by the known two-step deprotection procedure. Spectral data of compounds **21** and **24** were matched with those reported by Kim's group in 2004 in their synthesis of pancratistatin, thus completing the formal synthesis of pancratistatin.[5i,j]

A formal total synthesis of pancratistatin was accomplished in 14 steps from commercially available *m*-dibromobenzene (12 operations) via advanced intermediates from our previously described synthesis of narciclasine.[13] The crucial reductive transposition of **8a** to **9a** by the use of Myers' protocol worked nicely and this result bodes well for the eventual conversion of natural narciclasine (obtained by extraction of daffodil bulbs) to pancratistatin. We will report on this conversion and the comparison of its efficiency with the Pettit's synthesis in due course.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588515.

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(13) Experimental Procedures for **8a**, **9a**, and **18a**.
Methyl {(3a*S*,4*R*,7*R*,7a*R*)-7-Hydroxy-7′-methoxy-2,2-dimethyl-3a,4,7,7a-tetrahydro(5,5′-bibenzo[*d*][1,3]dioxol)-4-yl}carbamate (**8a**; see ref 7): The solution of enone **7a** (50 mg, 0.13 mmol) in MeOH (0.5 mL) was degassed with a stream of argon

for 15 min. After addition of cerium (III) chloride heptahydrate (71 mg, 0.19 mmol) the reaction mixture was stirred for 20 min, then cooled to 0 °C and sodium borohydride (6 mg, 0.14 mmol) was added in 2 portions. The reaction mixture was allowed to warm slowly to r.t. and stirred for 3 h. The reaction mixture was diluted with EtOAc (5 mL) and the grey precipitate was filtered through a plug of Celite. After concentration under reduced pressure the product was purified by preparative TLC (hexanes–EtOAc, 1:1) to furnish **8a** as a white foamy oil (48 mg, 96%).

Compound **8a**: R_f 0.2 (hexanes–EtOAc, 1:1); $[\alpha]_D^{24}$ –61.6 (*c* = 0.8, $CHCl_3$) {lit. $[\alpha]_D^{25}$ –14.4 (*c* = 0.8, $CHCl_3$)}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.57 (m, 2 H), 6.08 (s, 1 H), 5.96 (s, 2 H), 4.67 (dd, *J* = 10.6, 6.3 Hz, 3 H), 4.55 (s, 1 H), 4.41 (d, *J* = 10.2 Hz, 1 H), 3.89 (s, 3 H), 3.68 (s, 3 H), 2.77 (d, *J* = 10.3 Hz, 1 H), 1.34 (s, 3 H), 1.30 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.6, 149.3, 143.7, 137.3, 135.4, 133.7, 130.8, 109.4, 105.7, 101.8, 100.1, 75.3, 66.7, 56.8, 52.6, 51.1, 29.8, 26.3, 24.8.

Methyl {(3a*S*,4*R*,5*R*,7a*R*)-7′-Methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydro(5,5′-bibenzo[*d*][1,3]dioxol)-4-yl}carbamate (**9a**; see ref. 14): Allylic alcohol **8a** (629 mg, 1.60 mmol), triphenylphosphine (839 mg, 3.20 mmol), 2-nitro-*N*′-(propan-2-ylidene)benzenesulfonohydrazide (IP-NBSH; 823 mg, 3.20 mmol) was charged into Schlenk flask and kept under high vacuum for 1 h, then dissolved in THF (6 mL). Reaction mixture was cooled to 0 °C and di-*tert*-butyl azadicarboxylate (DBAD; 737 mg, 3.20 mmol) solution in THF (3 mL) was added dropwise. The reaction mixture was allowed to warm slowly to r.t. and stirred for 8 h. The reaction mixture was cooled to 0 °C and the mixture of 2,2,2-trifluoroethanol (3 mL) and H_2O (3 mL) was added dropwise and stirred for 16 h whereupon it was evaporated and submitted to two consecutive chromatographical columns [10 wt% deactivated silica gel, hexanes–EtOAc (1:1), then CH_2Cl_2–MeOH, 100:1]. The product was obtained as a white foamy glassy oil (345 mg, 64%).

Compound **9a**: R_f 0.1 (hexanes–EtOAc, 1:1); $[\alpha]_D^{24}$ +14.3 (*c* = 0.9, $CHCl_3$). IR (neat): 3331, 2984, 2936, 1705, 1607, 1524, 1475, 1071, 1048 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.36 (s, 1 H), 6.34 (s, 1 H), 5.90–6.01 (m, 4 H), 4.68 (m, 1 H), 4.62 (m, 1 H), 4.42 (m, 1 H), 3.87 (s, 3 H), 3.56 (s, 4 H (methyl group plus NH)), 3.38 (s, 1 H), 1.54 (s, 3 H), 1.41 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.6, 149.0, 143.7, 136.3, 135.6, 134.3, 123.7, 109.8, 107.5, 102.3, 101.6, 76.0, 72.6, 57.3, 56.7, 52.1, 45.8, 28.4, 26.1.

Methyl {(3a*S*,4*R*,5*R*,6*S*,7*S*,7a*R*)-6,7-Dihydroxy-7′-methoxy-2,2-dimethyl-3a,4,5,6,7,7a-hexahydro-(5,5′-bibenzo[*d*][1,3]dioxol)-4-yl}carbamate (**18a**): Olefin **9a** (1.35 g, 3.579 mmol) was dissolved in 20 mL of acetone and 5 mL of H_2O. Then OsO_4 (250 mg, 0.9834 mmol) and *N*-methylmorpholine-*N*-oxide (NMO, 419 mg, 3.579 mmol) were added. The reaction mixture was stirred at r.t. for 4 d, then quenched with sat. $NaHSO_3$ solution (20 mL). The reaction mixture was filtered through a plug of Celite, filtrate was concentrated, the residue was adsorbed on 10 wt% deactivated silica, and subjected to purification by column chromatography (hexanes–EtOAc, 1:2). Diol **18a** was isolated as a white foamy oil (785 mg, 53%)

Compound **18a**: R_f 0.1 (hexanes–EtOAc = 1:2); $[\alpha]_D^{25}$ –55.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.44 (s, 2 H), 5.96 (s, 2 H), 4.60 (s, 1 H), 4.26–4.45 (m, 2 H), 4.19 (s, 1 H), 3.81–4.04 (m, 5 H), 3.54 (s, 3 H), 2.92 (s, 1 H), 2.65 (s, 1 H), 1.82 (s, 1 H), 1.60 (s, 3 H), 1.39 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.7, 149.4, 144.0, 134.8, 132.1, 109.4, 102.5, 101.7, 77.6, 76.6, 72.7, 69.5, 56.7, 55.1, 52.3, 48.3, 29.9, 28.1, 26.0. Anal. Calcd for $C_{19}H_{25}NO_9$: C, 55.47; H, 6.13. Found: C, 54.80; H, 6.44.

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