STUDIES ON THE TOTAL SYNTHESIS OF GRANATICIN: SYNTHESIS OF (±)-7-DEOXY-GRANATICIN 12-O-METHYL ETHER FROM CHRYSAZIN

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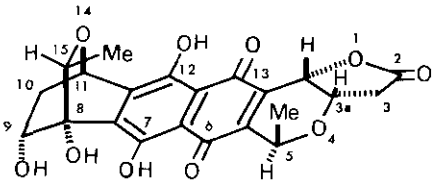
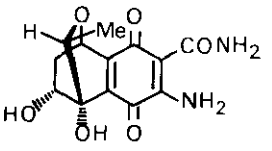
Abstract - The title compound (27) has been synthesized starting with chrysazin (1,8-dihydroxyanthraquinone) via 10-methoxy-8-(methoxy)methoxy-1-anthracenone (9). The strategy involves a stepwise and stereoselective construction of the oxabicycle and pyranolactone systems upon 9.

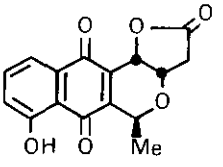
The naphthoquinone antibiotic granaticin (1), originally isolated from the culture of Streptomyces olivaceus in 1957[1] and since detected in a number of other actinomycetes, is active against Gram-positive bacteria and protozoa and exhibits significant antitumor activity against P-388 lymphocytic leukemia in mice.[2] Of noteworthy in the structure 1, which had been determined by a combination of chemical degradation and X-ray analysis in 1968,[3] is that granaticin can be regarded as a structural hybrid composed of sarubicin A (2)[4] and nanaomycin D (3)[5] in their C-glycoside derived oxabicycle[6] and pyrano-γ-lactone systems, respectively. Our interest in this novel molecule has led us to embark on a program directed towards its total synthesis.



granaticin (1)



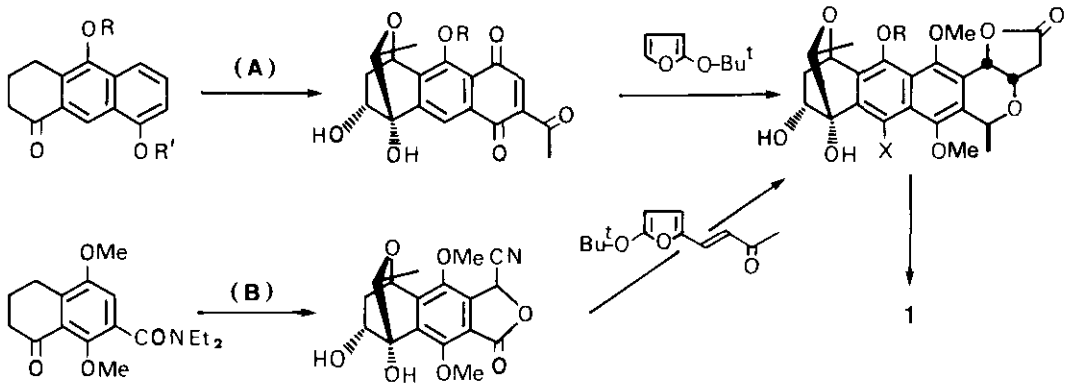
sarubicin A (2)



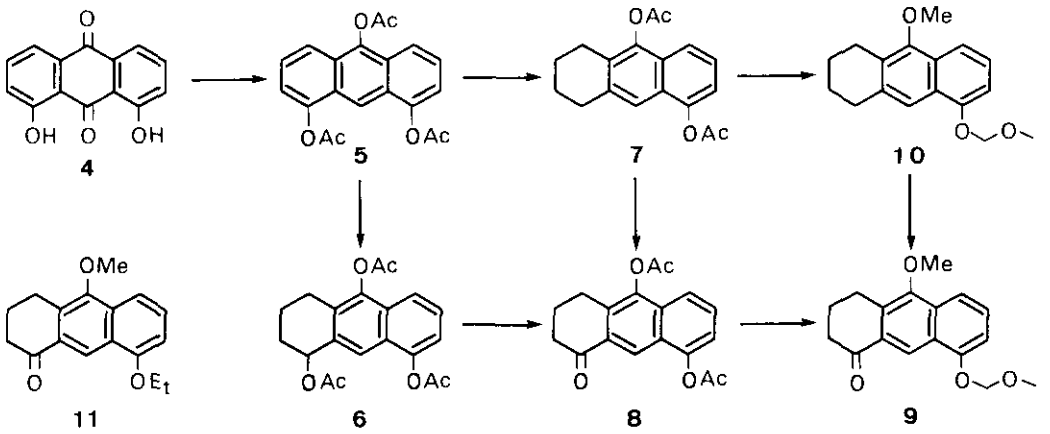
nanaomycin D (3)

The Scheme I illustrates the outline of two synthetic approaches to **1** that we envisioned based on our preliminary investigations. With regard to the preparation of the oxabicycle moiety, both routes (A & B) utilize the methodology that has been introduced by us for the total synthesis of **2**.[7] For the construction of the pyrano-γ-lactone moiety, on the other hand, the method of Kraus and Roth[8] should meet our strict requirements: mildness of the reactions involved, which does not affect the preformed oxabicycle, and high stereoselectivity as improved by us.[9] All other methods so far reported in nanaomycin synthesis,[10] which involve an acid-catalyzed epimerization of the benzylic C-Me, are not adaptable, since the oxabicycle would not survive under the reaction conditions. Here we report the first synthesis of the title compound having the complete skeleton of **1** by the route A.

Scheme I



Scheme II

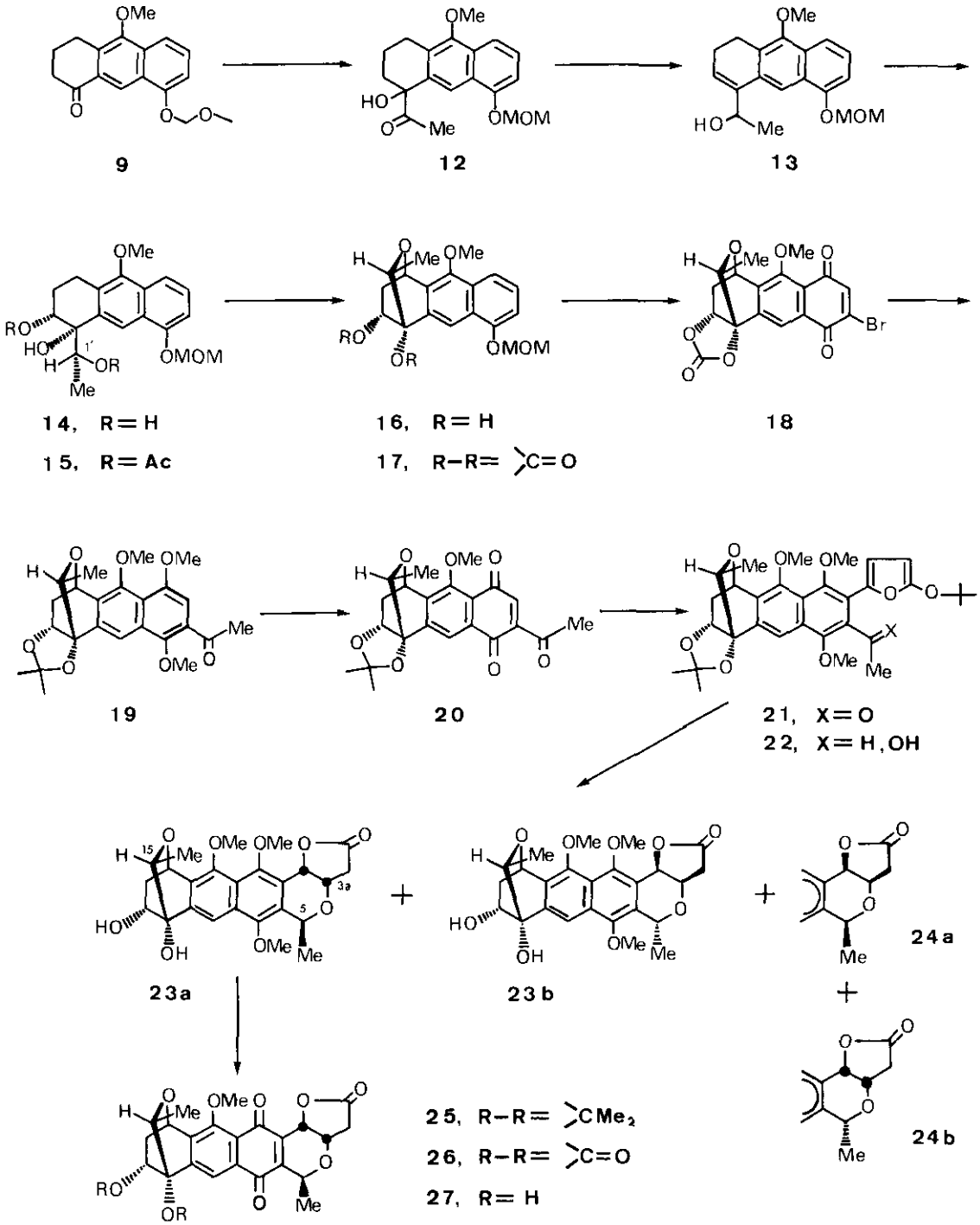


Chrysazin (**4**), the starting material in this investigation, was first converted in three steps (75% yield) to triacetoxyanthracene (**5**) according to the procedures described in the literature.[11] Extensive investigation on the partial hydrogenation of **5** has established the conditions leading to either tetrahydro compound (**6**) in 54% yield (5% Rh-Pd-C/AcOEt, 20 atm, room temp.) or its hydrogenolysis product **7** in 65% yield (5% Rh-C/AcOEt, 95 atm, 140°C). The compound **6** was transformed into diacetoxyanthracenone (**8**) in 80% yield by the following manipulation of the benzylic 1-acetoxy group: i) trifluoroacetolysis (TFA, room temp., 1 h); ii) ethanolysis of the resulting trifluoroacetate (EtOH, Et_3N, 0°C, 2 h); iii) oxidation of the liberated 1-hydroxy function (PCC, 4A sieves, CH_2Cl_2, 0°C to room temp.). The ketone **8** was also obtained from **7** in 63% yield by a regioselective benzylic oxidation with 3,5-dimethylpyrazole-CrO_3 complex.[12] It was then converted to 10-methoxy-8-(methoxy)methoxy-1-anthracenone (**9**) in 65% yield by a stepwise O-alkylation involving selective hydrolysis of the less hindered 8-acetate group: i) 1 eq 1.5% KOH-EtOH, 0°C; ii) $MeOCH_2Cl$, NaH, DMF; iii) 3% KOH-EtOH, room temp.; iv) Me_2SO_4, 6% KOH, CH_2Cl_2, n-Bu_4NBr). Alternatively, **9** was obtained from **7** in 55% yield by carrying out the stepwise O-alkylation first (formation of **10** in 80% yield) and then DDQ oxidation in MeOH[13] at room temperature (Scheme II). The structure of **9** was confirmed by its conversion to **11** (deprotection of the MOM group followed by O-ethylation), which was identical with an authentic sample prepared from 1-ethoxy-5-hydroxynaphthalene.[14]

With a ready access to the dialkoxyanthracenone **9** being established, construction of 5,6-naphtho-2-oxabicyclo[2.2.2]octene system was initiated by transformation into the allyl alcohol **13** (Scheme III), which was performed by three steps in 77% overall yield as follows: i) reaction with CH_2=C(OMe)Li followed by acid workup to give the α-ketol **12** (87%), ii) $NaBH_4$ reduction of **12** in iso-PrOH, iii) trifluoroacetic acid-catalyzed dehydration of the crude diol in CH_2Cl_2 (4 eq TFA, 0.14 M) at room temperature (88% yield from **12**). cis-Dihydroxylation of **13** by a catalytic osmylation (0.1 eq OsO_4, 6 eq Me_3NO, aqueous tert-BuOH, 60°C) produced a diastereomeric mixture of triols, **14** and its 1'-epimer, which were separable on their di-O-acetates by silica gel chromatography to provide **15** (83%) and its 1'-epimer (2.5%). The triol **14**,[15] which was obtained as a gelatinous mass by hydrolysis of its acetate **15**, was subjected to NBS mediated cyclization (10^{-2}M **14** in CCl_4, 1 eq NBS, 2 eq cyclohexene oxide, 0.1 eq AIBN, 40°C by sunlamp, 20 min) to afford **16**[15] in 81% chromatoghraphed yield.

Transformation of **16** into the acetonaphtoquinone **20**, that is required for attachment of the pyranolactone functionality, was nicely achieved as follows. Treatment of the carbonate **17** with 4 eq NBS in aqueous AcOH at 50°C for 30 min produced the bromoquinone **18**[15] in 78% yield. The position of the bromine atom as indicated in the structure (Scheme III) was assigned based on the

Scheme III


9
12
13
14, R=H
15, R=Ac
16, R=H
17, R–R= >C=O
18
19
20
21, X=O
22, X=H,OH
23a
23b
24a
24b
25, R–R= >CMe2
26, R–R= >C=O
27, R=H

presumed reaction mechanism, which would be the same in principle as that suggested for the case of 1,5-diacetoxynaphthalene.[16] Replacement of the bromine atom with acetyl group was then carried out by the following sequence of reactions via a lithio intermediate: i) reductive O-methylation (aqueous $Na_2S_2O_4$/AcOEt; then Me_2SO_4/K_2CO_3/acetone, reflux, 70%); ii) exchange of the carbonate group for isopropylidene group (MeOH-KOH; then CH_2=C(OMe)Me, CSA, 92%); iii) acetylation (n-BuLi, -78°C; $CeCl_3$,[17] Ac_2O at -100°C, 71%). The compound **19** thus obtained was subjected to oxidative demethylation employing Rapoport's procedure (4 eq AgO/HNO_3)[18] to generate the acetonaphthoquinone **20.** This sensitive quinone was, without purification, allowed to react with 2 eq 2-tert-butoxyfuran in dry acetone (-70 to -10°C, 80 min). The acetone solution of the resulting Michael adduct was refluxed for 80 min with 2.5 eq Me_2SO_4 in the presence of 3 eq K_2CO_3, thereby producing **21** in 54% yield from **20.**

Formation of the pyrano-γ-lactone system was now commenced by $LiAlH_4$ reduction of the ketone function in **21** (Et_2O, -50 to -30°C). The product, a diastereomeric mixture of the carbinols **22**, was subjected to the deprotection-cyclization sequence according to a modification[9] of the Kraus' protocol as follows: i) γ-naphthylbutenolide formation by treatment with 1 eq TsOH in MeCN (room temp., ca. 8 min; quenching immediately after **22** had been consumed); ii) pyran-ring closure with 1 eq DBU in toluene-CH_2Cl_2 (1:1) at -10°C for 10 min. There was obtained a ca. 4:4:1:1 mixture of four diastereomeric pyranolactones that possess the complete carbon skeleton of granaticin, in 55-60% overall yield from **21.** These isomers could have been separated by MPLC (10μ silica gel, AcOEt/hexane=2:1) in pure states. Assignment of the major two isomers to **23a,b** (3a,5-trans) and the minor two to **24a,b** (3a,5-cis), based on the known preference of the trans product in such annulation,[9] was supported by ^{1}H-nmr analysis (270 MHz),[15] diagnostic signals being those of C_{3a}-H (δ 4.77 for **23a,b**; δ 4.40 for **24a,b**) and C_5-H (δ 5.38 for **23a,b**; δ 5.07 for **24a,b**) on the pyranolactone group. Although **23a** (less polar) and **23b** (more polar) can be differentiated from each other by the resonances of of C_{15}-CH_3 in the oxabicycle (δ 0.81 and 0.87, respectively), the difference is too small to provide any information on their stereochemistry. The structures were, therefore, determined by X-ray analysis which was performed on the acetonide of **23b.**[19]

The compound **23a**, which has the same stereochemistry as **1**, could be oxidized with ceric ammonium nitrate[20] after protection of the 1,2-glycol system as acetonide or carbonate to furnish the corresponding naphthoquinones **25** or **26.** Brief treatment of **25** with TsOH in MeCN afforded **27**, (±)-7-deoxygranaticin 12-O-methyl ether.[15] At this point we encountered major difficulties in O-demethylation of **27**, the first and yet essential step for oxidation to the naphthazarin system in **1.** Reaction of BCl_3 with **26** occurred preferentially at the oxabicycle leading to a clean cleavage of the benzylic C_{11}-O bond. Attempt for nucleophilic demethylation with MeSLi[21] resulted in the

destruction of the pyranolactone system. Thus, use of a chemoselectively removable protecting group for the phenolic C_{12}-OH should be considered to accomplish the total synthesis of **1**. Investigations along this line are in progress in our laboratory.

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REFERENCES AND NOTES

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15. ^{1}H-nmr spectral data (270 MHz, $CDCl_3$), δ in ppm from TMS.
14: 1.07 (d, J = 6.6 Hz, 3H), 2.00 (dddd, J = 13.3, 9.5, 9.1, 5.4 Hz, 1H), 2.09 (dddd, J = 13.3,5.9, 5.4, 3.8 Hz, 1H), 2.81 (ddd, J = 17.3, 9.5, 5.9 Hz, 1H), 2.9 (br, 1H, OH), 3.2 (br, 1H,OH), 3.24 (dt, J = 17.3, 5.4 Hz, 1H), 3.54 (s, 3H), 3.8 (br, 1H, OH), 3.89 (s,

3H),4.36 (dd,J = 9.1, 3.8 Hz,1H), 4.50 (q, J = 6.6 Hz, 1H), 5.36, 5.39 (ABq, = 6.6 Hz, each 1H),7.06 (d, J = 8.2 Hz,1H), 7.38 (t, J = 8.2 Hz, 1H), 7.68 (d, = 8.2 Hz, 1H), 8.24 (s, 1H).
16:0.80 (d,J = 6.2 Hz, 3H), 1.49 (dt, J = 14.5, 1.4 Hz, 1H), 2.02 (br s, 1H, OH), 2.86 (ddd,J = 14.5, 8.9, 3.8 Hz, 1H), 3.32 (br s, 1H, OH), 3.53 (s, 3H), 3.89 (q, J = 6.2 Hz, 1H), 3.95 (s, 3H),4.01 (dd,J = 8.9, 1.4 Hz, 1H), 5.26 (dd, J = 3.8, 1.4 Hz, 1H), 5.36 (s, 2H),7.16 (d, J = 8.1 Hz, 1H), 7.42 (t, J = 8.1 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 8.21 (s, 1H).
18: 0.77 (d, J = 6.2 Hz, 3H), 1.68 (dd, J = 13.8, 5.9 Hz, 1H), 3.02 (ddd, J = 13.8, 9.5, 4.9 Hz, 1H), 3.95 (s, 3H), 4.40 (q, J = 6.2 Hz, 1H), 4.81 (dd, J = 9.5, 5.9 Hz, 1H), 5.45 (d, J = 4.9 Hz, 1H), 7.48 (s, 1H), 8.25 (s, 1H).
23a: 0.81 (d, J = 6.2 Hz, 3H), 1.59 (d, J = 6.6 Hz, 3H), 1.62 (d, J = 14.7 Hz, 1H), 2.73 (d, J = 17.5 Hz, 1H), 2.85 (s, 1H, OH), 2.97 (ddd, J = 14.7, 8.8, 3.7 Hz, 1H), 3.00 (dd, J = 17.5, 4.8 Hz, 1H), 2.9-3.1 (br, 1H, OH), 3.90 (s, 3H), 3.96 (s, 3H), 3.98 (q, J = 6.2 Hz, 1H), 4.00 (s, 3H), 4.15 (d, J = 8.8 Hz, 1H), 4.77 (dd, J = 4.8, 2.9 Hz, 1H), 5.33 (d, J = 3.7 Hz, 1H), 5.38 (q, J = 6.6 Hz, 1H), 5.64 (d, J = 2.9 Hz, 1H), 8.02 (s, 1H).
23b: 0.87 (d, J = 6.0 Hz, 3H), 1.55 (d, J = 6.8 Hz, 3H), 1.55 (d, J = 14.5 Hz, 1H), 1.65 (br s, 1H, OH), 1.8 (br, 1H, OH), 2.72 (d, J = 17.5 Hz, 1H), 2.98 (ddd, J = 14.5, 8.8, 3.7 Hz, 1H),3.00 (dd, J = 17.5, 4.8 Hz, 1H), 3.84 (s, 3H), 3.97 (q, J = 6.0 Hz, 1H), 3.97 (s, 3H), 4.01 (s, 3H), 4.14 (d, J = 8.8 Hz, 1H), 4.77 (dd, J = 4.8, 2.7 Hz, 1H), 5.35 (d, J = 3.7 Hz, 1H), 5.37 (q, J = 6.8 Hz, 1H), 5.63 (d, J = 2.7 Hz, 1H), 8.02 (s, 1H).
24a (less polar isomer): 0.86 (d, J = 6.2 Hz, 3H), 1.57 (d, J = 14.8 Hz, 1H), 1.74 (d, J = 6.3 Hz, 3H), 2.78 (d, J = 17.2 Hz, 1H), 2.94 (dd, J = 17.2, 4.0 Hz, 1H), 2.97 (ddd, J = 14.8, 7.1, 2.4 Hz, 1H), 2.9-3.1 (br, 2H, OH), 3.87 (s, 3H), 3.92 (s, 3H), 3.99 (q, J = 6.2 Hz, 1H), 4.03 (s, 3H), 4.12 (d, J = 7.1 Hz, 1H), 4.40 (dd, J = 4.0, 2.4 Hz, 1H), 5.07 (q, J = 6.3 Hz, 1H), 5.33 (d, J = 2.4 Hz, 1H), 5.63 (d, J = 2.4 Hz, 1H), 8.09 (s, 1H).
24b (more polar isomer): 0.81 (d, J = 6.2 Hz,3H), 1.61 (d, J = 14.5 Hz, 1H), 1.77 (d, J = 6.3 Hz, 3H), 2.79 (d, J = 17.4 Hz, 1H), 2.94 (dd, J = 17.4, 4.4 Hz, 1H), 2.98 (ddd, J = 14.5, 7.1,2.2 Hz, 1H), 2.85-3.0 (br, 2H, OH), 3.85 (s, 3H), 3.87 (s, 3H), 3.97 (q, J = 6.2 Hz, 1H), 4.02 (s, 3H), 4.19 (d, J = 7.1 Hz, 1H), 4.40 (dd, J = 3.9, 2.5 Hz, 1H), 5.07 (q, J = 6.3 Hz, 1H), 5.35 (d, J = 2.2 Hz, 1H), 5.61 (d, J = 2.5 Hz, 1H), 8.07 (s, 1H).
27 (mp 261-3°C): 0.79 (d, J = 6.2 Hz,3H),1.52 (d,J = 12.6 Hz, 1H), 1.56 (d, J = 6.7 Hz, 3H), 2.71 (d, J = 17.6 Hz, 1H), 2.93 (ddd, J = 12.6, 8.8, 3.1 Hz, 1H), 2.93 (s, 1H, OH), 2.95 (s,1H, OH), 2.98 (dd, J = 17.6, 5.2 Hz,1H), 3.93 (q, J = 6.2 Hz, 1H), 3.93 (s, 3H), 4.12 (d,J = 8.8 Hz, 1H), 4.69 (dd, J = 5.2, 3.1 Hz, 1H), 5.05 (q, J = 6.7 Hz, 1H), 5.29 (d, J = 3.1 Hz, 2H), 8.16 (s, 1H).

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19. Crystals suitable for diffraction measurements were obtained by slow evaporation of iso-Pr_2O at room temperature, mp 277-9°C. Crystal data; $C_{28}H_{32}O_9$, FW = 512.5, monoclinic, space group $P2_1/c$, a = 8.765(4), b = 11.335(3), c = 26.563(6) Å, β = 102.28(2)°, U = 2579(1) Å^3, D_c = 1.32 gcm^{-3}, Z = 4. The structure was solved by direct methods and refined by a block-diagonal least-squares technique to R = 0.042.

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