

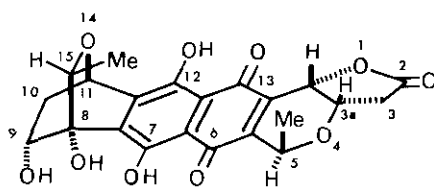
STUDIES ON THE TOTAL SYNTHESIS OF GRANATICIN: SYNTHESIS OF (+)-7-DEOXY-
GRANATICIN 12-O-METHYL ETHER FROM CHRYSAZIN

Keiichi Nomura, Kozo Hori, Makoto Ishizuka, and Eiichi Yoshii*

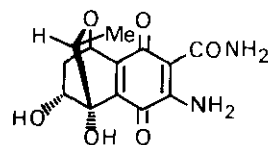
Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical
University, Toyama 930-01, Japan

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 oxabicyclic and pyranolactone systems upon 9.

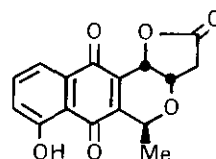
The naphthoquinone antibiotic granaticin (1), originally isolated from the culture of *Streptomyces olivaceus* in 1957¹ and since detected in a number of other actinomycetes, is active against Gram-positive bacteria and protozoa and exhibits significant antitumor activity against P-388 lymphocytic leukemia 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 oxabicyclic⁶ 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)



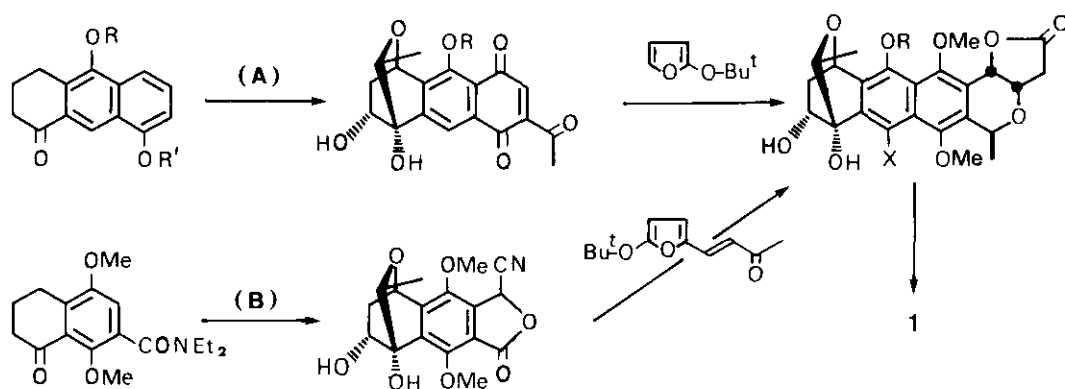
sarubicin A (2)



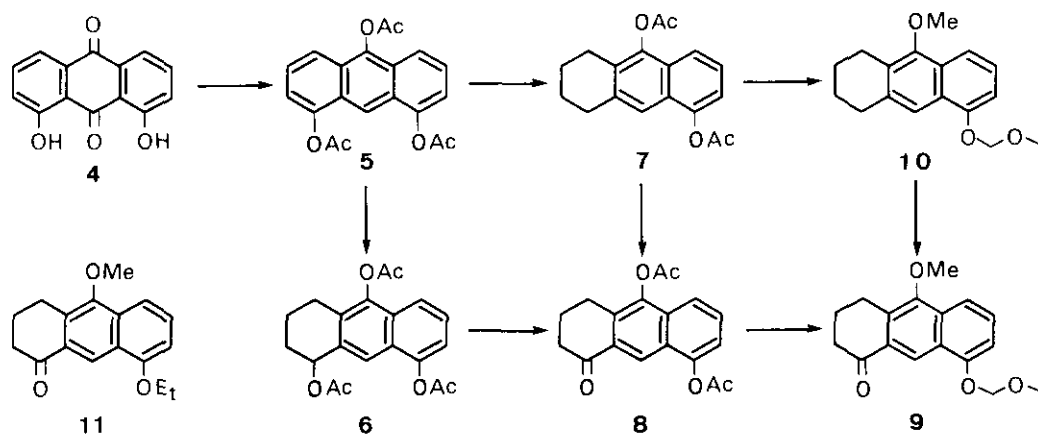
nanaomycin D (3)

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 oxabicyclic 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 Roth⁸ should meet our strict requirements: mildness of the reactions involved, which does not affect the preformed oxabicyclic, 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 oxabicyclic 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

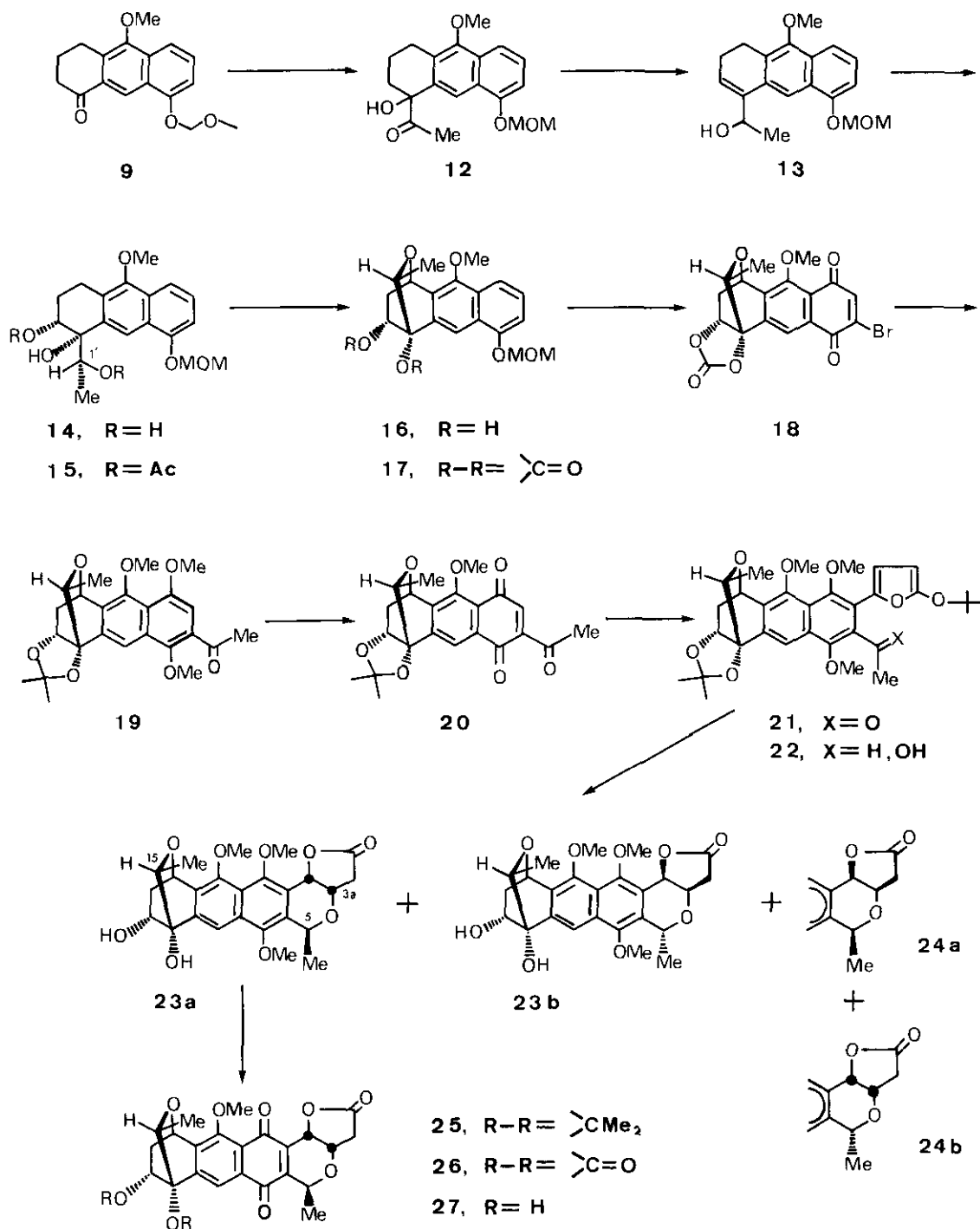


Chrysazin (4), the starting material in this investigation, was first converted in three steps (75% yield) to triacetoxyanthracene (5) according to the procedures described in the literature.¹¹ Extensive investigation on the partial hydrogenation of 5 has established the conditions leading to either 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, Et₃N, 0°C, 2 h); iii) oxidation of the liberated 1-hydroxy function (PCC, 4A sieves, CH₂Cl₂, 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-CrO₃ 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) MeOCH₂Cl, NaH, DMF; iii) 3% KOH-EtOH, room temp.; iv) Me₂SO₄, 6% KOH, CH₂Cl₂, *n*-Bu₄NBr). 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 MeOH¹³ 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 CH₂=C(OMe)Li followed by acid workup to give the α -ketol 12 (87%), ii) NaBH₄ reduction of 12 in iso-PrOH, iii) trifluoroacetic acid-catalyzed dehydration of the crude diol in CH₂Cl₂ (4 eq TFA, 0.14 M) at room temperature (88% yield from 12). *cis*-Dihydroxylation of 13 by a catalytic osmylation (0.1 eq OsO₄, 6 eq Me₃NO, 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 (10⁻²M 14 in CCl₄, 1 eq NBS, 2 eq cyclohexene oxide, 0.1 eq AIBN, 40°C by sunlamp, 20 min) to afford 16¹⁵ in 81% chromatographed yield.

Transformation of 16 into the acetoneaphthoquinone 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 18¹⁵ in 78% yield. The position of the bromine atom as indicated in the structure (Scheme III) was assigned based on the

Scheme III



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 $\text{Na}_2\text{S}_2\text{O}_4/\text{AcOEt}$; then $\text{Me}_2\text{SO}_4/\text{K}_2\text{CO}_3/\text{acetone}$, reflux, 70%); ii) exchange of the carbonate group for isopropylidene group (MeOH-KOH ; then $\text{CH}_2=\text{C}(\text{OMe})\text{Me}$, CSA, 92%); iii) acetylation ($n\text{-BuLi}$, -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 modification⁹ 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 (10 μ silica gel, $\text{AcOEt}/\text{hexane}=2:1$) 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 ^1H -nmr analysis (270 MHz),¹⁵ diagnostic signals being those of $\text{C}_{3a}\text{-H}$ (δ 4.77 for **23a,b**; δ 4.40 for **24a,b**) and $\text{C}_5\text{-H}$ (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 $\text{C}_{15}\text{-CH}_3$ in the oxabicyclo (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 acetone of **23b**.¹⁹

The compound **23a**, which has the same stereochemistry as **1**, could be oxidized with ceric ammonium nitrate²⁰ 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**, ($\pm$)-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 oxabicyclo leading to a clean cleavage of the benzylic $\text{C}_{11}\text{-O}$ 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 C₁₂-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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 15. ¹H-nmr spectral data (270 MHz, CDCl₃), 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, $J = 6.6$ Hz, each 1H), 7.06 (d, $J = 8.2$ Hz, 1H), 7.38 (t, $J = 8.2$ Hz, 1H), 7.68 (d, $J = 8.2$ 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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