

SYNTHETIC STUDIES OF SESQUITERPENES WITH A CIS-FUSED DECALIN SYSTEM, 6.¹ ISOLATION, STRUCTURE ELUCIDATION, AND SYNTHESIS OF NORSESQUIBENIHIOL AND THE SYNTHESIS OF DEHYDROCHAMAECYNENOL

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ABSTRACT.—Norsesquibenihol, a new norsesquiterpene alcohol, was isolated from the essential oil of *Chamaecyparis formosensis* and its structure was elucidated as **8** by spectroscopic methods. Allylic rearrangement of the 3 β - and 3 α -alcohols **18** and **19**, which were derived from the known acetylenic ketone **9** in three steps, gave a mixture of **8** and dehydrochamaecynenol [**6**]. The structure of norsesquibenihol [**8**] was therefore proved by this synthesis.

During the course of the investigation of the terpenoid constituents of Benihi wood (*Chamaecyparis formosensis* Matsum., Cupressaceae) in the late 1960s, Nozoe *et al.* isolated the novel norsesquiterpenes, chamaecynone [**1**], isochamaecynone [**2**], hydroxyisochamaecynone [**3**], chamaecynenol [**4**], chamaecynenol acetate [**5**], dehydrochamaecynenol [**6**], and dehydrochamaecynenal [**7**] (Figure 1), as the first examples of acetylenic terpenoids (2–4). In the present study, compounds **1–3** have been synthesized from α -santonin (5–8).

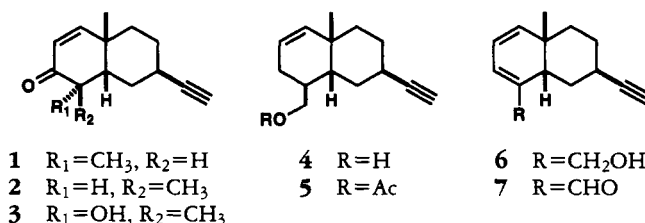


FIGURE 1

In 1971, Kondo *et al.* examined the role of essential oils in the resistance of coniferous woods to termites and found that those of the genus *Chamaecyparis* showed a high resistance to termite attack (9). In 1973, the same group isolated the termiticidal principles of the essential oils and identified them as **1** and **2** (10).

Recently, we undertook a re-investigation of these compounds because of an interest in their structure-termiticidal activity relationships. This paper deals with the isolation and characterization of a new acetylenic norsesquiterpene named norsesquibenihol [**8**], and its synthesis from the known acetylenic ketone **9** (5,7), for a definitive structure proof.

RESULTS AND DISCUSSION

The acetylenic norsesquiterpene alcohol **8** was isolated from a fraction [bp 113–116° (1.8 Torr)] of the essential oil of Benihi wood by cc on Si gel. The pure alcohol **8** is quite unstable and gives an amorphous solid on standing. The eims of **8** showed a M⁺ at *m/z*

¹For Part 5, see Ando *et al.* (1).

202, in agreement with a molecular formula of $C_{14}H_{18}O$. The uv (MeOH) absorption of **8**, λ max 234 nm (log ϵ 4.26), indicated the presence of a *s*-trans conjugated diene. The ir (neat) spectrum of **8** showed absorptions at 3401, 1053 (-OH), 3322, 2119 (-C \equiv CH), 1667, 1603, 886, and 814 (*s*-trans conjugated diene). The nmr spectrum (60 MHz, in CCl_4) of **8** showed signals at δ 0.80 (3H, s, CH_3), 1.98 (1H, d, $J=2.5$ Hz, -C \equiv CH), 2.80 (H-C-C \equiv CH), 4.38 (1H, $W_{b/2}=7.0$ Hz, H-C-OH), 4.90 (2H, \sphericalangle C=CH $_2$), 5.53 (1H, $J=10.0$ and 3.0 Hz, H-C=C-H), and 6.06 (1H, $J=10.0$ and 2.0 Hz, H-C=C-H).

On the basis of the above spectral data of **8** and the occurrence of **6** and related acetylenic norsesquiterpenes with *cis*-eudesmane skeletons in the same essential oil, the gross structure of norsesquibenihiol can be drawn as shown in structure **8** (Figure 2).

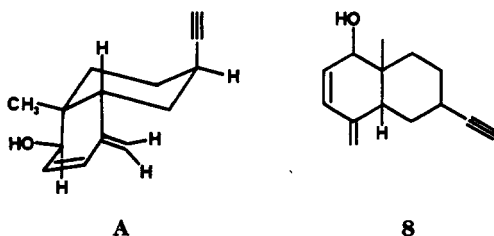
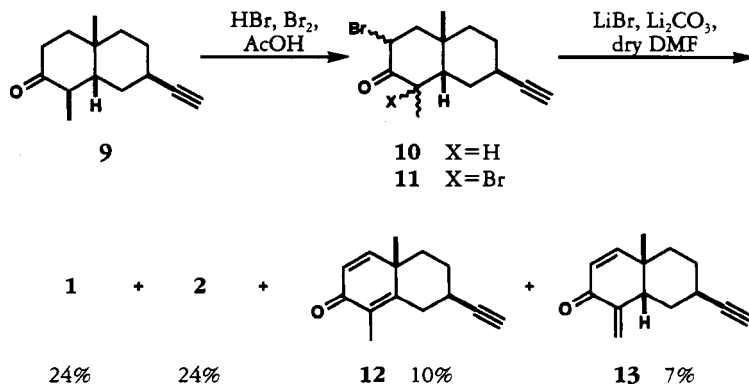


FIGURE 2

In the 1H -nmr spectrum of **8**, the observed coupling constants ($J_{1,2}$ =ca. 3 Hz, $J_{1,3}$ =ca. 2 Hz) and the half-band width ($W_{b/2}=7.0$ Hz) of H-1 showed that OH-1 was affixed in a β -equatorial manner. The half-band-width of H-7 ($W_{b/2}=10$ Hz) showed that the ethynyl group at C-7 is β -axial. Therefore, the stereo-structure **A**, possessing a novel non-steroid *cis*-fused eudesmane skeleton with a β (*eq*)-OH group at C-1 and a β (*ax*)-ethynyl group at C-7, was proposed for **8**.

The synthesis of **8** was attempted with the objective of establishing a definite structure for this compound. Bromination of **9** (5,7) with 1 equivalent of Br_2 in the presence of HBr in AcOH gave an unstable mixture of α -monobromoketones [**10**] and α,α' -dibromoketones [**11**], which was directly treated with LiBr and Li_2CO_3 in DMF at 155° to give **1**, **2**, dehydrochamaecynone [**12**], and isodehydrochamaecynone [**13**] in 24%, 24%, 10%, and 7% yields, respectively (Scheme 1).

The structures of **1**, **2**, and **12** were determined by comparison of their spectral and physical data with those of authentic samples, whose syntheses have already been



SCHEME 1

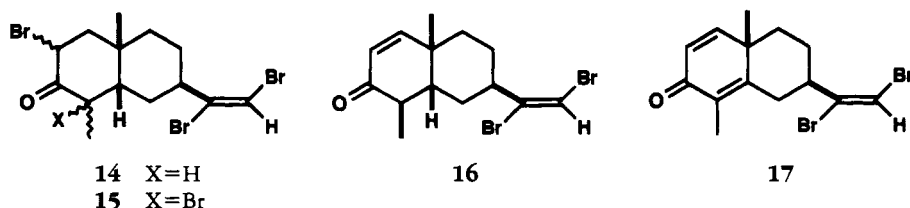


FIGURE 3

reported by this laboratory (5,7). The fourth and least abundant compound, **13**, which has been named isodehydrochamaecynone, was the starting material for the following synthesis of norsesquibenihol [**8**].

An attempt at bromination of **9** with 2 equivalents of Br_2 gave a complex mixture of **10**, **11**, **14**, and **15**. Dehydrobromination of this unstable mixture of bromides gave addition products of Br_2 to the triple bond such as **16** and **17** along with **1**, **2**, and **12**, and the yield of the desired **13** was not improved (Figure 3).

The structure of **13** was determined by the analysis of its ^1H -nmr spectrum (200 MHz, in CDCl_3) as shown in Figure 4. The non-steroid conformation of **13** was demonstrated by the long-range coupling constant between H-1 and H-5 ($J_{1,5}=2.1$ Hz).

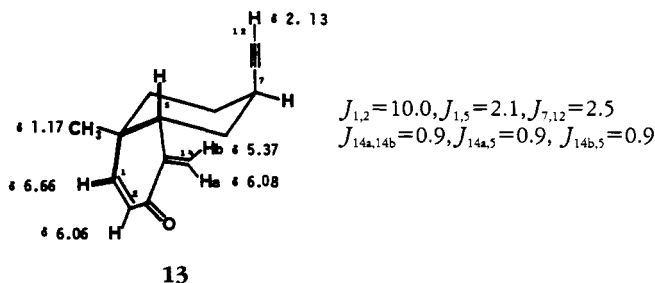
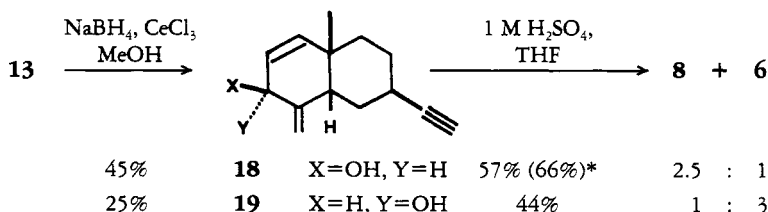


FIGURE 4

Reduction of **13** with NaBH_4 in the presence of CeCl_3 in MeOH gave a β -alcohol [**18**] and an α -alcohol [**19**] (Scheme 2). The structures of **18** and **19** were determined by analysis of their ^1H -nmr spectra (200 MHz, in CDCl_3), as shown in Figure 5. The stereochemical assignments of OH-3 of **18** and **19** were determined by comparison of the vicinal coupling constants ($J_{2,3}$) and the allylic long-range coupling constants ($J_{1,3}$ and $J_{3,14a}$) of these compounds. The $\alpha(ax)$ -configuration of OH-3 of **19** was also demonstrated by the large downfield shift of H_{ax} -6 of **19** compared with the analogous data of **18**.



*The yield in parentheses is based on the recovered starting material.

SCHEME 2

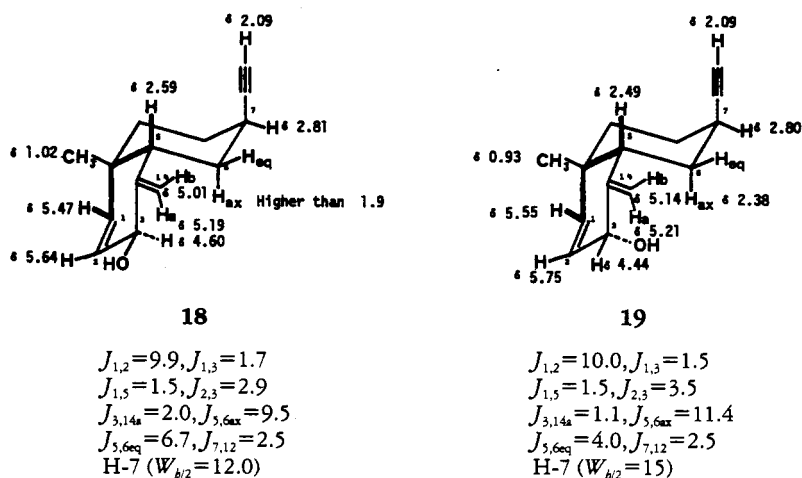


FIGURE 5

Treatment of the 3β -alcohol **18** with 1 M H_2SO_4 in THF at room temperature gave a 2.5:1 mixture of the 1β -hydroxy-2,4(14)-diene derivative **8** and the 14-hydroxy-1,3-diene derivative **6** in 57% yield (Scheme 2). In contrast, treatment of the 3α -alcohol **19** with 1 M H_2SO_4 under the same conditions gave a 1:3 mixture of **8** and **6** in 44% yield.

The 1H -nmr spectrum of synthetic **8** was identical with that of natural norsesquibenihol as shown in Table 1, and the 1H -nmr spectrum of synthetic **6** was identical with that of natural dehydrochamaecynenol (**3**), as shown in Table 2. It is remarkable that the long-range coupling between H-1 and H-5 was not observed in the 1H -nmr spectrum of synthetic **8** recorded at 200 MHz in CCl_4 (see stereo-structure **A** or **8** in Figure 2). This observation strongly supported the $\beta(eq)$ -configuration of the hydroxy group at C-1, which had been deduced from the $J_{1,2}$ and $J_{1,3}$ values during the structure determination of **8**.

In conclusion, the structure of norsesquibenihol was determined as shown in structure **8** by the analysis of its spectral data as well as by its synthesis.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps are uncorrected. 1H -Nmr spectra were recorded at 200 MHz in $CDCl_3$, unless otherwise stated. Coupling constants are in Hz. Mass spectra (eims) were recorded

TABLE 1. 1H -Nmr Data for **8**.

Proton	Natural Product ^a (60 MHz, in CCl_4)	Synthetic (200 MHz, in CCl_4)
	δ (J in Hz)	δ (J in Hz)
1	4.38 (m, $W_{b/2}=7$)	4.36 (m, $W_{b/2}=7.0$)
2	5.53 (dd, $J=10$ and 3)	5.51 (dm, $J=10.0, W_{b/2}=5.0$)
3	6.06 (dd, $J=10$ and 2)	6.01 (dd, $J=10.0$ and 2.0)
5		2.50 (dd, $J=12.0$ and 5.5)
7	2.80 (m, $W_{b/2}=10$)	2.81 (m, $W_{b/2}=10.0$)
12	1.98 (d, $J=2.5$)	1.97 (d, $J=2.5$)
14	4.90 (br s, $W_{b/2}=4$)	4.88 (br s, $W_{b/2}=4.3$)
15	0.80 (s)	0.80 (s)

^aBecause the isolation of the natural product was carried out many years ago and the sample was quite unstable, the nmr data we have are 1H -nmr spectra recorded by a 60 MHz instrument.

TABLE 2. $^1\text{H-Nmr}$ Data for **6**.

Proton	Natural Product ^{a,b} (100 MHz in CDCl_3)	Synthetic (200 MHz in CDCl_3)
	δ (J in Hz)	δ (J in Hz)
1	5.40 (dm, $J=9.0$, $W_{b/2}=4.0$)	5.41 (dm, $J=9.2$, $W_{b/2}=3.3$)
2	5.92 (dd, $J=9.0$ and 5.0)	5.91 (dd, $J=9.2$ and 5.0)
3	5.85 (m, $W_{b/2}=8.0$)	5.84 (dm, $J=5.0$, $W_{b/2}=2.6$)
7	2.72 (m, $W_{b/2}=10.0$)	2.74 (m, $W_{b/2}=10.0$)
12	2.03 (d, $J=2.5$)	2.06 (d, $J=2.5$)
14	4.13 (br s, $W_{b/2}=2.5$)	4.13 (m, $W_{b/2}=8.2$)
15	0.91 (s)	0.92 (s)

^aBecause the isolation of **6** was carried out several years ago, the $^1\text{H-nmr}$ data of this natural product were recorded at 100 MHz.

^bSee Takase *et al.* (3).

at 70 eV. Reactions were run under an atmosphere of N_2 . DMF was dried by removing the $\text{C}_6\text{H}_6/\text{H}_2\text{O}$ azeotrope and stored over 4 Å sieves. THF was distilled from sodium benzophenone ketyl. To describe hplc conditions, solvent, flow rate in ml/min, and retention time (R_t) in min are designated in turn. A 250×4 mm i.d. stainless steel column packed with 10 μm Si gel was employed for hplc.

PLANT MATERIAL.—*Chamaecyparis formosensis* Matsum. (Japanese name "Benihi") was collected at Mt. Chilan Shan, Ilan Hsien Province, 50 km south of Taipei, Taiwan, Republic of China, in December 1963. The estimated age of the tree when the collection was made was 250 years.

EXTRACTION AND ISOLATION.—The branches (of 30-cm diameter) and the aerial part of the roots (of 30-cm diameter) of peeled Benihi wood were chopped into small pieces and extracted with hexane. The concentrated extracts were subjected to steam distillation. The distillate was extracted with Et_2O . The extracts were dried and concentrated. The residue was distilled *in vacuo* by a distillation apparatus with a spinning band column. The fraction distilled at $113\text{--}116^\circ$ (1.8 Torr) gave a mixture containing acetylenic norsesquiterpenes. Rapid elution of a Si gel column [EtOAc-hexane (1:9)] of the distillation fraction gave a new norsesquiterpene named norsesquibenihiol [**8**] as an unstable colorless oil: uv (MeOH) λ_{max} (log ϵ) 234 nm (4.26); ir ν_{max} (neat) 3401, 3322, 2119, 1667, 1603, 1053, 886, 814 cm^{-1} ; $^1\text{H-nmr}$ data, see Table 1; eims (70 eV) m/z M^+ 202 (31), 187 (55), 184 (13), 169 (42), 159 (92), 145 (59), 91 (100), 77 (72), 43 (92).

PREPARATION OF CHAMAECYNONE [**1**], ISOCHAMAECYNONE [**2**], DEHYDROCHAMAECYNONE [**12**], AND ISODEHYDROCHAMAECYNONE [**13**] FROM **9** (WITHOUT PURIFICATION OF INTERMEDIATES **10** AND **11**).—To a solution of **9** (30 mg, 0.147 mmol) in AcOH (3 ml) were successively added 48% HBr (30 μl) and a solution of Br_2 (24 mg, 0.15 mmol) in AcOH (0.3 ml). The mixture was stirred for 1.5 h at room temperature, poured into saturated aqueous NaCl (20 ml), and extracted with Et_2O (3×20 ml). The combined extracts were washed successively with 2 M aqueous Na_2CO_3 (3×20 ml) and saturated aqueous NaCl (2×30 ml), dried (Na_2SO_4), and concentrated to give an oily crude product (41 mg). A mixture of this crude product (41 mg, 0.15 mmol), and Li_2CO_3 (43 mg, 0.58 mmol), LiBr (43 mg, 0.49 mmol) in DMF (3 ml) was heated at 155° for 5.5 h and worked up in the usual manner to give an oily crude product (26 mg), which was passed through Si gel [4 g, EtOAc-hexane (5:95)].

The first eluent (0–60 ml) gave a mixture of **1**, **2**, and **13** (21 mg). The second eluent (61–150 ml) gave **12** (3 mg, 10%) as colorless crystals (pentane): mp 84° (7).

The mixture of **1**, **2**, and **13** (21 mg) was then further purified by hplc [EtOAc-hexane (5:95), 3.0 ml/min]. The first peak (R_t 5.0) gave **1** (7.0 mg, 24%) as colorless crystals (pentane): mp 88° (5,7). The second peak (R_t 5.6) gave **13** (2 mg, 7%) as an oily material: $[\alpha]_D^{20} - 101^\circ$ ($c=0.09$); ir (CHCl_3) ν_{max} 3316, 2952, 1672 cm^{-1} ; $^1\text{H-nmr}$ data, see Figure 4; hreims m/z 200.1196 ($\text{C}_{14}\text{H}_{16}\text{O}$ requires 200.1201). The third peak (R_t 6.4) gave **2** (7 mg, 24%) as colorless crystals: mp 79° (5,7).

REDUCTION OF **13** AND FORMATION OF **18** AND **19**.—A mixture of **13** (24 mg, 0.12 mmol), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (54 mg, 0.14 mmol) and NaBH_4 (5.4 mg, 0.14 mmol) was stirred for 10 min. The mixture was worked up as usual to give a crude oil (34 mg), which was then purified by hplc [EtOAc-hexane (1:9), 3.0 ml/min].

The first peak (R_t 5.6) gave **18** (11 mg, 45%) as colorless needles (pentane): mp 74° ; $[\alpha]_D^{20} + 1.7^\circ$ ($c=0.47$); ir (CHCl_3) ν_{max} 3600, 3448, 3096, 2112, 1654, 899 cm^{-1} ; $^1\text{H-nmr}$ data, see Figure 5; hreims m/z 202.1360 ($\text{C}_{14}\text{H}_{18}\text{O}$ requires 202.1358).

The second peak (*R*, 6.4) gave **19** (6 mg, 25%) as a colorless oil: $[\alpha]_D^{20} - 32^\circ$ ($c=0.37$); ir (CHCl₃) ν max 3616, 3464, 3316, 3100, 2112, 896 cm⁻¹; ¹H-nmr data, see Figure 5; hreims *m/z* 202.1361 (C₁₄H₁₈O requires 202.1358).

ALLYLIC REARRANGEMENT OF 18 AND FORMATION OF NORSEQUIBENIHIOL [8] AND DEHYDROCHAMAECYENOL [6].—A solution of **18** (3 mg, 0.015 mmol) in a mixture of THF (1 ml) and 1 M H₂SO₄ (0.45 ml, 0.45 mmol) was stirred at room temperature for 3 h, and poured into saturated aqueous NaCl (20 ml). The mixture was worked up as usual to give an oily crude material (6 mg), which was purified by hplc [EtOAc-hexane (1:9), 3 ml/min].

The first peak (*R*, 5.4) gave **18** (0.4 mg, 13%) as a colorless oil. The second peak (*R*, 6.4) gave an inseparable mixture of **8** and **6** (1.7 mg, 57%) as a colorless oil. The ratio of **8** and **6** was determined to be 2.5:1 by analysis of the ¹H-nmr spectrum of this mixture. The ¹H-nmr spectrum of **8** was determined by the analysis of this mixture inasmuch as **8** was the major component. ¹H-Nmr data (in CCl₄, locked by external D₂O in a capillary tube) of **8**, see Table 1; ¹H nmr (in CDCl₃) of **8** δ 0.85 (3H, s, Me-10), 2.12 (1H, d, *J*=2.5 Hz, H-12), 2.55 (1H, dd, *J*=11.8 and 5.2 Hz, H-5), 2.86 (1H, m, *W*_{*b*/2}=10.5 Hz, H-7), 4.45 (1H, m, *W*_{*b*/2}=13.8 Hz, H-1), 4.94 (1H, m, *W*_{*b*/2}=2.8 Hz, H-14), 5.59 (1H, dm, *J*=10.0 Hz, *W*_{*b*/2}=5.2 Hz, H-2), 6.10 (1H, dd, *J*=10.2 and 2.0 Hz, H-3).

ALLYLIC REARRANGEMENT OF 19 AND FORMATION OF NORSEQUIBENIHIOL [8] AND DEHYDROCHAMAECYENOL [6].—A solution of **19** (2 mg, 0.01 mmol) in a mixture of THF (1 ml) and 1 M H₂SO₄ (0.45 ml, 0.45 mmol) was stirred at room temperature for 5 h, and worked up as usual to give a crude oil (6 mg), which was passed through Si gel [4 g, EtOAc-hexane (1:9)]. The eluent was then purified by hplc [EtOAc-hexane (1:9), 3 ml] and the peak (*R*, 6.4 min) gave an inseparable 1:3 mixture of **8** and **6** (0.9 mg, 44%). Because **6** was the major component, the ¹H-nmr data of **6** were determined by the analysis of this mixture. ¹H-Nmr data of **6**, see Table 2.

***p*-NITROBENZOATES OF NORSEQUIBENIHIOL [8] AND DEHYDROCHAMAECYENOL [6].**—The mixture of a 2.5:1 mixture of **8** and **6** (1.7 mg, 0.0083 mmol), *p*-nitrobenzoyl chloride (1.8 mg, 0.0098 mmol), and 4-dimethylaminopyridine (1.2 mg, 0.0095 mmol) in pyridine (0.5 ml) was stirred for 24 h at room temperature and worked up in the usual manner to give a crude product (2.9 mg), which was passed through a column [Si gel (70–230 mesh); 5 g, EtOAc-hexane (5:95)]. The eluent was further purified by hplc [EtOAc-hexane (5:95), 3.0 ml/min].

The first peak (*R*, 2.4 min) gave the *p*-nitrobenzoate of **8** (1.7 mg, 58%) as colorless crystals (ether/hexane): mp 63°; ¹H nmr δ 1.06 (3H, s, Me-10), 2.13 (1H, d, *J*=2.4 Hz, H-12), 2.64 (1H, dd, *J*=12.0 and 5.0 Hz, H-5), 2.92 (1H, m, *W*_{*b*/2}=12.0 Hz, H-7), 5.04 (2H, br s, *W*_{*b*/2}=4.0 Hz, H-14), 5.55 (1H, dm, *J*=10.0 Hz, *W*_{*b*/2}=5.0 Hz, H-2), 6.02 (1H, m, *W*_{*b*/2}=6.0 Hz, H-1), 6.23 (1H, dd, *J*=10.0 and 2.0 Hz, H-3), 8.22 (2H, dd, *J*=7.0 and 2.0 Hz, *p*-NO₂Bz-H), 8.32 (2H, dd, *J*=7.0 and 2.0 Hz, *p*-NO₂Bz-H); hreims *m/z* 351.1507 (C₂₁H₂₁O₄N requires 351.1471).

The second peak (*R*, 3.0 min) gave the *p*-nitrobenzoate of **6** (0.8 mg, 27%) as colorless crystals (ether/hexane): mp 101°; ¹H nmr δ 0.96 (3H, s, Me-10), 2.05 (1H, d, *J*=2.6 Hz, H-12), 2.28 (1H, ddd, *J*=12.0, 5.0, and 1.0 Hz, H-5), 2.77 (1H, m, *W*_{*b*/2}=10.5 Hz, H-7), 4.87 (2H, s, H-14), 5.50 (1H, ddd, *J*=9.0, 1.4, and 1.0 Hz, H-1), 5.92 (1H, dd, *J*=9.0 and 6.0 Hz, H-2), 5.97 (1H, m, H-3), 8.24 (2H, dd, *J*=7.0 and 2.0 Hz, *p*-NO₂Bz-H), 8.32 (2H, dd, *J*=7.0 and 2.0 Hz, *p*-NO₂Bz-H); hreims *m/z* 351.1504 (C₂₁H₂₁O₄N requires 351.1471).

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