(hexane); IR (CH_2Cl_2) ν 1751 (C=O), 1732 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 9.88 (d, 1 H, J = 3.6 Hz, CHO), 7.25 (d, 2 H, J = 9 Hz, Ar), 6.87 (d, 2 H, J = 9 Hz, Ar), 4.49 (dd, 1 H, J = 6.1 Hz, J' = 3.6 Hz, CH), 3.79 (s, 3 H, OCH_3), 3.58 (m, 1 H, CH), 1.87 (m, 1 H, HCH), 1.72 (m, 1 H, HCH), 1.10 (dd, 3 H, J = 8.4 Hz, J' = 6.4 Hz, CH_3). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.57; H, 6.32; N, 5.78.

***cis*-4-Formyl-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (9).** The same procedure as above was followed, starting from *cis*-4-(hydroxymethyl)-3-isopropyl-1-(4-methoxyphenyl)-azetidin-2-one (7) (24.9 g, 0.1 mol), yield 19.8 g (80%): mp 96–98 °C (AcOEt/hexane); IR (KBr) ν 1749, 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 9.91 (d, 1 H, J = 4.2 Hz, CHO), 7.23 (d, 2 H, J = 9 Hz, Ar), 6.86 (d, 2 H, J = 9 Hz, Ar), 4.45 (dd, 1 H, J = 4.2 Hz, J' = 6.1 Hz, CH), 3.78 (s, 3 H, OCH_3), 3.37 (dd, 1 H, J = 6.1 Hz, J' = 10.8 Hz, CH), 2.20–2.08 (m, 1 H, CH), 1.22 (d, 3 H, J = 6.5 Hz, CH_3), 0.96 (d, 3 H, J = 6.5 Hz, CH_3). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00: H, 6.93; N, 5.66. Found: C, 68.42; H, 6.84; N, 5.69.

Acknowledgment. This work was supported by Comisión Interministerial de Ciencia y Tecnología (Project FAR:88-0393). Grants from the Eusko Jaurlaritza to J. M. Ontoria and from the Ministerio de Educación y Ciencia to J. M. Ordiozola are gratefully acknowledged.

Registry No. 1, 141-75-3; 2, 108-12-3; 3, 72079-55-1; *cis*-4, 127055-24-7; *trans*-4, 127055-25-8; *cis*-5, 128474-68-0; *trans*-5, 128474-79-3; *cis*-6, 128474-72-6; *cis*-7, 129374-75-0; *cis*-8, 128571-93-7; *cis*-9, 133505-01-8; (±)-PS-5, 92471-41-5; (±)-PS-6, 135682-87-0; DMSO, 67-68-5; 1-(4-methoxyphenyl)-3-(1-hydroxyethyl)-4-(1-methyl-2-phenylethenyl)azetidin-2-one, 100239-22-3; 1-allyl-3-ethyl-4-(hydroxymethyl)azetidin-2-one, 135614-56-1; 3-phenoxy-4-(4-methoxyphenyl)-1-(2-hydroxy-2-phenylethyl)azetidin-2-one, 93681-48-2; 2-[(*tert*-butyldimethylsilyl)oxy]propanol, 135614-57-2; 2-[(tri-*iso*-propylsilyl)oxy]-propanol, 135614-58-3; 2,2-dimethyl-3-(*tert*-butyloxycarbonyl)-4-(hydroxymethyl)-tetrahydro-oxazole, 108149-63-9; 3-phenoxy-4-(4-methoxyphenyl)-1-(phenylcarbonylmethyl)azetidin-2-one, 114497-93-7; 1-(4-methoxyphenyl)-3-acetyl-4-(1-methyl-2-phenylethenyl)azetidin-2-one, 123003-88-3; 1-allyl-3-ethyl-4-formylazetidin-2-one, 135614-59-4; 2-[(*tert*-butyldimethysilyl)-oxy]propanone, 87727-28-4; 2-[(tri-*iso*-propylsilyl)oxy]propanone, 135614-60-7; 2,2-dimethyl-3-(*tert*-butyloxycarbonyl)-4-formyl-tetrahydro-oxazole, 102308-32-7; bis(trichloromethyl)carbonate, 32315-10-9.

Supplementary Material Available: Experimental procedures and spectral data for products c–h listed in Table I and NMR spectra for products e and q (4 pages). Ordering information is given on any current masthead page.

Synthesis of (±)-Rubrynolide and a Revision of Its Reported Stereochemistry

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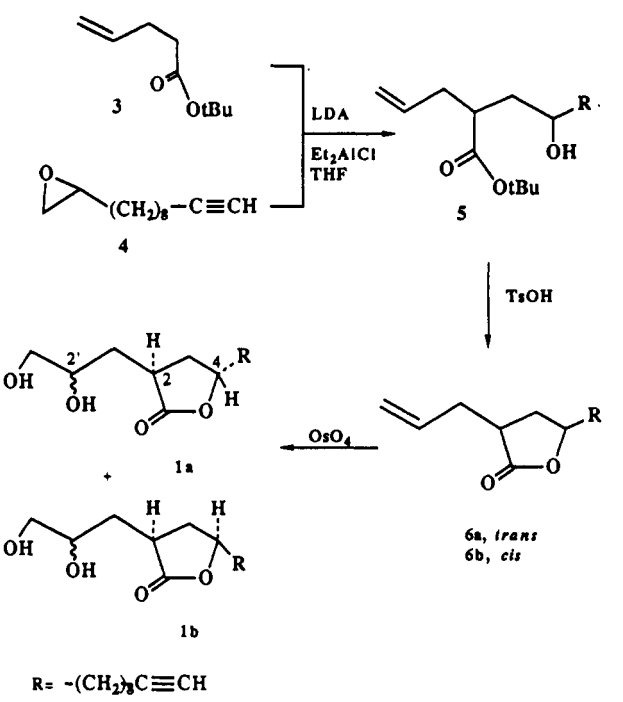
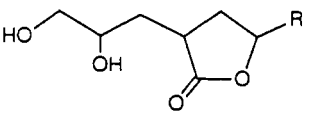
Rubrynolide (1) and rubrenolide (2), which represent a novel natural product type,[1] have been extracted as a 1:1 pair from the trunk of the Brazilian tree *Nectandra Rubra*.[1] Their biosynthesis has been discussed,[2] and they may represent interesting variants of biosynthetic routes to fatty acids.[1] An evaluation of their biological activity has been encouraged as a result of preliminary screening.[3] We herein describe the first synthesis of (±)-rubrynolide and confirm its proposed molecular connectivity.[1a] However, we revise the stereochemistry originally proposed for the 2,4-disubstituted lactone ring.[1b]

Scheme I





1, R = $(CH_2)_8$-C≡CH

2, R = $(CH_2)_8$-CH=CH_2

Our original plan was to synthesize both 1 and 2 from the enyne lactone 6 (Scheme I). Osmylation[4] of 6 would produce rubrynolide, and the selective reduction[5] of this product would produce rubrenolide. The key to this approach is a direct 1,3-asymmetric induction via an epoxide–aluminum enolate reaction that we demonstrated earlier.[6] The reported trans lactone stereochemistry could be achieved by reacting the favored *E* enolate of 3 with epoxide 4 (Scheme I). The ester enolate is of strategic importance here since, as a weak base, it will not abstract the acetylenic hydrogen of the epoxide and thereby cause side reactions.

The actual synthesis is outlined in Scheme I. The tosylate of 9-decen-1-ol (7) was treated with lithium acetylide–ethylene diamine complex. The resulting enyne 8 was epoxidized with *m*-CPBA. Epoxide 4 was then treated with the aluminum enolate[6] of *tert*-butyl 4-pentenoate to give predominantly the syn hydroxy ester 5 (syn/anti ratio

(1) (a) Franca, N. C.; Gottlieb, O. R.; Coxon, D. T.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1972**, 514. (b) Franca, N. C.; Gottlieb, O. R.; Coxon, D. T. *Phytochemistry* **1977**, *16*, 257.

(2) (a) Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1537. (b) Filho, R. B.; Diaz, P. P.; Gottlieb, O. R. *Ibid.* **1980**, *19*, 455.

(3) (a) Gottlieb, O. R.; Mors, W. B. *J. Agric. Food Chem.* **1980**, *28*, 196. (b) Gottlieb, O. R. *J. Ethnopharm.* **1979**, *1*, 309.

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(5) (a) Lindlar, H.; Dubnis, R. *Org. Synth.* **1962**, *46*, 89. (b) Tedeschi, R. J.; Clark, G., Jr. *J. Org. Chem.* **1962**, *27*, 4323.

(6) Sturm, T.-J.; Marolewski, A. E.; Taylor, S. K. *J. Org. Chem.* **1989**, *54*, 2039.

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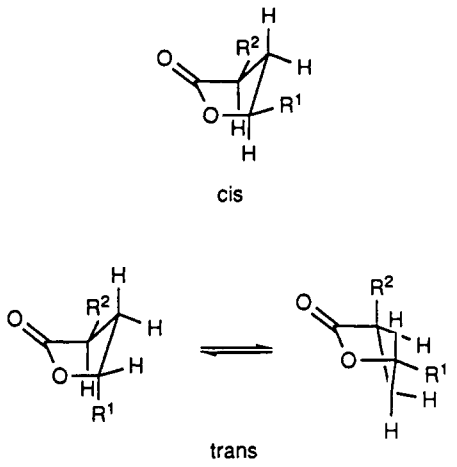


Figure 1. Cis- and trans-2,4 disubstituted γ-lactones.

of 85:15 based on cyclization to the lactone). Compound **5** was treated with *p*-toluenesulfonic acid by established methods[7] to give **6** (trans:cis = 85:15). This compound was then osmylated,[4] and an ^1H NMR spectrum of the product mixture (a major (**1a**) and a minor pair (**1b**) of racemates) was compared to authentic rubrynolide.

An authentic sample of rubrynolide exhibited ^1H and ^{13}C NMR spectra that matched those of a minor product (**1b**) of our synthesis. Earlier,[6] we unambiguously showed, by synthesis of known lactones,[8] that our aluminum enolate–epoxide products cyclize to give an 85:15 ratio of trans and cis lactones. We therefore suspected that rubrynolide was actually a cis-disubstituted lactone. Extensive NMR evidence (below) as well as our synthesis support this stereochemical assignment.

Despite numerous attempts, we were unable to separate the mixture of very polar isomeric diol products. Flash chromatography and even HPLC could not resolve the isomers. However, we were able to isolate a small amount of one of the crystalline trans lactones **1a** by crystallization from CH_2Cl_2/CCl_4, and it is identified below. Isomeric separation was achieved after acetylation of the product mixture (from which some trans lactone had been removed). The four isomeric acetates (**9–12**) were separated by HPLC and distinguished spectroscopically. The one (**9**) having the same HPLC retention time as acetylated rubrynolide (a known compound[1b]) was collected and analyzed in detail. Acetylated rubrynolide and this compound gave the same mass, IR, and 300-MHz NMR (^1H and ^{13}C) spectra. Also, the natural and synthetic acetylation products were mixed together in a 3:2 ratio and ^1H and ^{13}C NMR spectra were run on the mixture. The number and position of the peaks was unchanged, which confirms that the minor synthetic isomer was rubrynolide.

We had planned to make the chiral natural product when, based on the original report, we assumed that it was a trans lactone. Utilization of (*R*)-4 and asymmetric osmylation[9] in our synthetic scheme would give the reported isomer **1a**. However, since our method makes mainly the trans isomer and the natural product is actually a cis compound, we abandoned plans to make the chiral compound.

Table I. ^1H NMR Data for Rubrenolide and Rubrynolide[a]

resonance	proton chemical shift, ppm	coupling,[b] Hz	integral
H13″	5.81	17.0 (H12″), 10.3 (H11″), 6.7 (H10″)	0.96
H12″	4.99	17.2 (H13″), 1.85 (*H11″*), 1.85 (*H10″*)	1.0
H11″	4.93	10.1 (H13″), 1.60 (*H12″*), 1.60 (*H10″*)	1.0
H4	4.42	10.6 (H3a), 7.34 (H1″), 5.31 (H3e), 5.31 (H1″)	2.0
H2′	3.81	9.86 (H1e′), 6.57 (H3a′), 3.54 (H3a′), 3.04 (*H1a′*)	2.0
H3e′	3.66	10.9 (H3a′), 3.54 (H2′)	2.2
H3a′	3.51	10.9 (H3e′), 6.58 (H2′)	2.2
H2	2.92	12.4 (H3a), 8.35 (H3e), 7.09 (H1e′), 7.09 (H1a′)	1.9
H3e	2.53	12.5 (H3a), 8.40 (H2), 5.32 (H4)	2.0
H15″	2.18	7.08 (H14″), 2.78 (H16″)	1.7
H10″	2.04	7.1 (m)[f], 1.52 (*H12″*), 1.52 (*H11″*)	2.2
H1e″[c]	1.96	14.4 (H1e′), 9.86 (H2′), 7.09–7.34 (H2)	*d*
H16″[c]	1.94	2.5–2.8 (H15″)	*d*
H1e″	1.75	complex	2.2
H1a″[c]	1.6	complex	*e*
H3a[c]	1.59	12.4 (H3e), 12.4 (H2), 10.4 (H4)	*e*
H1a′[c]	1.62	14.4 (H1e′), 7.1 (H2), 3.29 (*H2′*)	*e*
H14″	1.52	7.34 (H15″), 7.34 (m)[f]	2.1

[a] The two isomers are present in a 1:1 ratio. [b] The coupled proton is given in parentheses. Corresponding cross-peaks are detected in the homonuclear COSY except for those that are italic. [c] Multiplets are overlapped. [d] Total integrated area equals 2.7. [e] Total integrated area equals 7.2. [f] Methylene group.

We analyzed the key NMR coupling constants of the enyne lactone **6** to be sure that our synthesis produced primarily a trans lactone. This compound has one less chiral center than **1** and hence there are fewer isomers to complicate the spectrum. The reported three-bond coupling constants[1b,8] for the hydrogens on carbons 2–4 of a 2,4-disubstituted lactone ring (Figure 1) are both approximately 6–7 Hz for the trans lactone, whereas for the cis lactone they are approximately 6 and 11 Hz. Both coupling constants of our major isomer were small (5.5 Hz), suggesting it was indeed the trans lactone. The minor isomer gave coupling constants of 5.6 and 12.9 Hz for these protons, suggesting it was the cis isomer.[10]

Since lactones are prevalent in nature,[11] it is important that this structure be corrected. For example, a recent product identification utilized ORD data on the proposed structures for rubrynolide and rubrenolide to determine the stereochemistry of bullatacinone (their structure would not be altered by the results of our work, however).[12] Another report[13] cites rubrenolide as containing a struc-

(7) (a) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Am. Chem. Soc.* **1986**, *108*, 5352. (b) Nakamura, E.; Kuwajima, I. *Ibid.* **1985**, *107*, 2138.

(8) Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1480.

(9) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Wai, J. S.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *Ibid.* **1989**, *111*, 1123. (c) Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041. (d) Corey, E. J.; Lotto, G. I. *Ibid.* **1990** *31*, 2665. (e) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. (f) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834.

(10) It is noteworthy that the authors[1b] who suggested that rubrynolide was a trans isomer actually reported coupling constants that were consistent with the cis isomer. They reported 5.5 and 11–12 Hz for the couplings of these rubrynolide protons. Their tabulated data[1b] suggest that model cis coupling constants are 5.7–6.0 and 10.8 Hz (which support a cis structure) and that trans coupling constants are 6.8–7.9 and 5.5–7.0 Hz in line with earlier work.[8] Thus, their data support a cis structure. The confusion may have arisen when the authors mistakenly listed their compounds **7** and **8** as the cis and trans isomers, respectively in the body of the paper whereas they were correctly listed (vice versa) in Table I. They reported **1** and **2** as trans compounds in later articles.[2,3]

(11) For a review, see: Kane, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1980**, *14*, 661.

(12) Hui, Y.-H.; Ruprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. Z.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463.

(13) Kunz, T.; Janowitz, A.; Reissig, H.-U. *Chem. Ber.* **1989**, *122*, 2165.

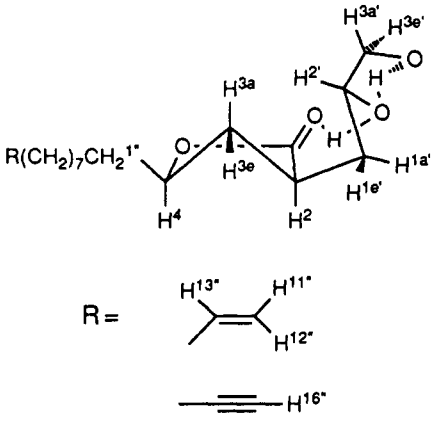


Figure 2. Hydrogen-bonded structure of rubrenolide/rubrynolide.

tural unit frequently encountered in natural products.

NMR Structural Assignments

The NMR spectra of rubrenolide, $C_{17}H_{30}O_4$, and rubrynolide, $C_{17}H_{28}O_4$, are identical with the exception of the allyl and propargyl terminal groups. The structure and relative stereochemistry were assigned using homonuclear COSY and characteristic coupling constants from resolution enhanced spectra on the mixture of natural products. The results (Table I) agree with the structural assignment of Coxon et al.,[1b] but their assignment of the trans configuration for the 2,4-disubstituted γ-lactone does not account for the large couplings of H2 and H4 to the geminal proton H3a (12.4, 10.6 Hz). Trans-2,4-disubstituted γ-lactones typically exhibit small vicinal couplings (5–7 Hz) as a consequence of ring flipping. Cis-substituted lactones[8,13] show two large vicinal couplings to H3a since both substituents prefer pseudoequatorial positions[14] (Figure 1). Vicinal coupling constants of 10–12 Hz for H3a with H4 have been observed in other cis lactones.[13] The cis configuration of rubrynolide/rubrenolide establishes the relative stereochemistry as 2*S* and 4*R*.[10] The observed couplings in the diol side chain are consistent with a predominant hydrogen-bonded conformer. The 1,2-diol is held in a five-membered ring and a second hydrogen bond to the lactone holds this side chain in a seven-membered boat conformation (Figure 2). Thus, the relative stereochemistry at C2′ is established as 2′*S* and so rubrenolide is 2′*S*,2*S*,4*R*. A positive Cotton effect has been observed on this lactone,[1b] and Fracna[1b] et al. have applied the Hudson lactone rule[15] to this compound to suggest that the C4 is *R*.[1b] Beecham[16] has suggested that a positive Cotton effect indicates the β-carbon is above the plane of the ring (see Figure 2). If these conventions hold, they both suggest that the absolute configuration is 2′*S*,2*S*,4*R*.

The major synthetic diol **1a** proved to be a diastereomer of rubrynolide, as determined from a homonuclear COSY experiment and coupling constants. The chemical shifts and the coupling constants of the glycol side chain are nearly identical for both rubrynolide and the synthesized isomer (Tables I and II). However, the couplings of the lactone ring differ significantly. The resonance H2 of the synthetic diol is a triplet of triplets, with couplings of 9.28 and 7.32 Hz. Assignment of the couplings of H2 to the AB pair, H3a and H3e, requires H4 to be coupled to the same resonances by 3.3 and 7.8 Hz, respectively. A trans-substituted γ-lactone accounts for the observed couplings and for the significant reduction of the chemical shift difference between the resonances 3a and 3e ($\Delta\nu$ 0.07 ppm) as compared to that of rubrynolide/rubrenolide $\Delta\nu$ 0.94 ppm). The geminal protons are conformationally averaged in the trans structure. Assuming the same hydrogen-bonding networks as before, the relative stereochemistry of the trans isomer is 2′*S*,2*S*,4*S*.

The four diacetylated compounds **9**–**12** isolated from the reaction were identified as diastereomers based on ^{13}C NMR, ^1H NMR, and IR data. This is in accord with the synthesis that produces three chiral centers in the final product **1**. The stereochemical assignment of each of the

Table II. ^1H NMR Data for Trans Diol

resonance	proton chemical shift, ppm	coupling,[a] Hz	integral
H4[b]	4.57	9.4 (H1a″), 7.8 (H3e), 4.0 (H1e″), 3.3 (H3a)	1.0
H2′	3.84	9.77 (H1e′), 6.60 (H3a′), 3.42 (H3e′), 3.42 (H1a′)	0.98
H3e′	3.67	11.23 (H3a′), 3.42 (H2′)	0.98
H3a′	3.51	11.23 (H3e′), 6.60 (H2′)	0.99
H2	2.92	9.28 (H3e), 9.28 (H3e), 7.32 (H1a′), 7.32 (H1e′)	1.2
H15″	2.18	6.9 (m),[e] 2.4 (H16″)	*c*
H3e	2.17	12.5 (H3e), 9.3 (H2), 3.45 (H4)	*c*
H3a	2.10	12.5 (H3a), 9.4 (H2), 7.5 (H4)	*c*
H16″	1.95	2.5 (H15″)	*d*
H1e′	1.93	14.65 (H1a′), 9.77 (H2′), 7.82 (H2)	*d*
H1a″, H1e″, H1a′	1.65–1.79	complex	

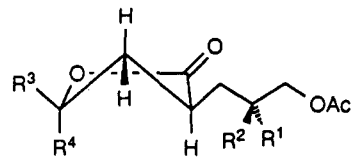
[a] The coupled proton is given in parentheses. Corresponding cross-peaks are detected in the homonuclear COSY. [b] Coupling constants determined by spin–spin simulation. [c] Multiplets are overlapped, total integrated area equals 4.0. [d] Total integrated area equals 2.2. [e] Methylene group.

Table III. ^1H NMR of Acetylated Rubrynolide Isomers

	9[a]		10		11		12	
resonance	δ	*J*	δ	*J*	δ	*J*	δ	*J*
H2′	5.14	3.42[t]	5.15	3.42[t]	5.21	3.42	5.2[c]	3.4
		6.35		6.35		5.37[t]		5.5
		10.26		10.25		8.3		8.5[t]
H4	4.34	5.87[t]	4.52	4.9[t]	4.49	4.88[t]	4.33	5.37[t]
		7.33		7.8[t]		7.81[t]		7.33
		11.24						10.26
H3e′	4.26	3.42	4.27	3.42	4.28	3.41	4.28	3.42
		11.72		11.72		12.21		12.21
H3a′	4.04	6.35	4.05	6.35	4.05	5.86	4.05	5.86
		11.72		11.72		12.21		12.21
H2	2.63[b]	3.0	2.64	3.9	2.69	5.37	2.67	5.0
		8.6		8.79[t]		8.79[q]		8.79[t]
		10.4		11.23				12.5
		11.4						
H3e	2.55[b]	5.4					2.45	5.37
		8.6						8.9
		12.5						12.7
H1e′	2.34	3.14	2.25	3.91				
		10.26		10.26				
		14.1		14.6				
H15″	2.19	2.7	2.18	2.44	2.17	2.93	2.19	2.93
		7.3[t]		6.83[t]		7.32[t]		6.84[t]
H16″	1.95	2.70[t]			1.94	2.69[t]	1.95	2.44[t]
H1a′					1.82	8.79[t]	1.77	8.79[t]
						14.65		14.4

[a] Spectrum identical with that obtained for diacetylated rubrynolide. [b] An AB pair, couplings obtained from simulated spectra. [c] Complex pattern, couplings obtained from simulated spectra.

(14) Kaime, C.; Ortuno, M. R.; Font, J. *J. Org. Chem.* **1986**, *51*, 3946.
(15) Klyne, W.; Scopes, P. M.; Williams, A. *J. Chem. Soc.* **1965**, 7237.
(16) Beecham, A. F. *Tetrahedron Lett.* **1968**, 2355.



9:
R1 = H
R2 = OAc
R3 = $C_{10}H_{19}$
R4 = H

10:
R1 = H
R2 = OAc
R3 = H
R4 = $C_{10}H_{19}$

11:
R1 = OAc
R2 = H
R3 = H
R4 = $C_{10}H_{19}$

12:
R1 = OAc
R2 = H
R3 = $C_{10}H_{19}$
R4 = H

Figure 3. Acetylated diastereoisomers.

diastereomers is based on the ^1H NMR data (Table III). Only a partial analysis has been achieved because of severe overlap problems in the aliphatic region. The spectra of isomer **9** are identical with those of the diacetylated rubrynolide. The coupling pathway can be traced along the diacetylated glycol chain for **9** and reveals that H2 is coupled to H1e′ by 3.1 Hz and to H3e by 8.6 Hz. The remaining two couplings, 11.4 and 10.4 Hz, are attributed to the unresolved protons H3a and H1a′.

Only the 5.87-Hz coupling of H4 to H3e can be definitively assigned, but the assignment of the large 11.24-Hz coupling to H3a is in accord with the cis stereochemistry for the lactone. The relative stereochemistry of C2′ for **9** could not be determined due to lack of the hydrogen-bonding network. But based on the assignment of its diol precursor, **9** is assigned the 2′*S*,2*S*,4*R* structure (Figure 3).

The four diastereomers **9**–**12** differ structurally by the relative stereochemistry between C2 and C4 (cis/trans lactone) and between C2 and C2′. The close similarities of chemical shifts and coupling constants allow pairwise groupings of functionalities. The side-chain shifts and couplings identify **9** and **10** as a pair and hence the side chain of **10** has the same stereochemistry as the diol in rubrynolide. The trans lactone geometry was established above for the diol precursor to **10**. Thus, **10** is the diacetate of the trans lactone diastereomer with a relative configuration 2′*S*,2*S*,4*S*. The second pairwise linkage is shown in the couplings of the ring protons H2 and H4. Diastereomers **9** and **12** show a large and an intermediate coupling to H3a and H3e, respectively, consistent with the cis lactone. The equal couplings of H2 with H3e and H3a and of H4 with H3a and H3e in **10** and **11** indicate the trans lactone. This then established that **12** has the same 2,4 linkage as rubrynolide and hence must be the 2′*R*,2*S*,4*R* compound. The final assignment of **11** as the 2′*R*,2*S*,4*S* compound is then fully consistent with these interrelationships.

Experimental Section[17,18]

The 2D NMR spectroscopy was performed on 300- and 500-MHz instruments. THF used in the reactions was distilled from sodium/benzophenone immediately before use. Dry DMSO was purchased from Aldrich Chemical Co. HPLC separations were done using a 25 cm × 9.2 mm 10-μM silica gel column. With one exception, satisfactory (±0.4%) combustion analyses were obtained for all new compounds. For the compound lacking a satisfactory C,H analysis (**1a**), a melting point, high-resolution MS, and a ^{13}C NMR spectrum are provided to prove product purity. Details of the syntheses of **3** and **7** are included in the supplementary material.

1-Dodecen-11-yne (8). Under N_2, 20.0 g (67 mmol) of **7** was added over 20 min to a mixture of 6.92 g of lithium acetylide–ethylenediamine complex (74 mmol) and 100 mL of dry DMSO at 10–15 °C.[19] After the solution was stirred 1.5 h at 25 °C, 50 mL of H_2O was added dropwise to the cooled mixture. The organic layer was collected, and the aqueous layer was extracted three times with 100 mL of hexane. The combined organic layers were dried ($MgSO_4$), concentrated, and distilled using a 6-in. Vigreux column to give 4.84 g of **8** (44%): bp 59–61 °C (1.1–1.2 mm); ^1H NMR ($CDCl_3$) δ 1.2–1.4 (m, 10 H), 1.46 (quintet, 2 H, J = 7.4 Hz), 1.88 (t, 1 H, J = 2.9 Hz), 2.01 (q, 2 H, J = 7.4 Hz), 2.13 (t of d, 2 H, $J_{1,2}$ = 7.3 Hz, $J_{1,3}$ = 2.9 Hz), 4.8–5.0 (m, 2 H), 5.7–5.84 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.98, 29.1, 29.3, 29.5, 29.7 (2 C) 30.0, 34.4, 68.7, 84.9, 114.7 and 139; IR (NaCl disks) 3420 (s, alkyne CH), 3080 (m), 2120 (w), 990 (m), 910 (s) cm^{-1}; MS m/e (relative intensity) 121 (8), 93 (32), 81 (45), 79 (63), 67 (67), 55 (65), 41 (100), 39 (55). Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.99; H, 12.46.

1,2-Epoxy-11-dodecyne (4). A solution of 4.59 g (21 mmol) of 80–85% pure *m*-CPBA in 120 mL of CH_2Cl_2 was added dropwise over 1.75 h to 3.4 g (20 mmol) of **8** in 80 mL of CH_2Cl_2. Stirring was continued for 30 min, and then the mixture was refluxed 1 h and stirred overnight at rt. The mixture was cooled with an ice bath, and 40 mL of pentane was added. The resulting white precipitate was removed and washed with pentane by vacuum filtration. The organic filtrate was washed three times with saturated $NaHSO_3$ and 5% $NaHCO_3$ and once with 15% NaCl. The dried ($MgSO_4$) and concentrated oil was distilled to give 3.06 g (82%) of **4**: bp 55–57 °C (0.025–0.015 mm); ^1H NMR ($CDCl_3$) δ 1.0–1.5 (m, 14 H), 1.73 (t, 1 H, J = 2.4 Hz), 1.93 (t of d, 2 H, $J_{1,2}$ = 5.7 Hz, $J_{1,3}$ = 2.4 Hz), 2.19 (m, 1 H), 2.46 (t, 1 H, J = 4.4 Hz), 2.64 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.8, 26.4, 28.9, 29.2, 29.3, 29.4, 29.9, 32.9, 47.1, 52.4, 68.8, 84.6. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.04; H, 11.28.

***tert*-Butyl 4-Hydroxy-2-(2-propenyl)-13-tetradecynoate (5).** At −78 °C, under N_2, 1.6 mL (11 mmol) of dry diisopropylamine was added dropwise to a solution of 30 mL of dry THF and 5.5 mL (11 mmol) of 2.08 M *n*-butyllithium in hexane. After 30 min, 1.78 g (11 mmol) of **3** was added dropwise at −78 °C.[6] The solution was allowed to warm to −40 °C over 30 min and then 11.5 mL (11.5 mmol) of 1 M Et_2AlCl in hexane was added dropwise. After the solution was stirred for 30 min, 0.87 g (4.3 mmol) of epoxide **5** was added dropwise and the mixture was stirred 5 h at −40 °C. Saturated NH_4Cl (30 mL) was added to the cooled solution, and the resulting mixture was added to a mixture of 50 mL of 6 M HCl and 50 g of ice. The organic layer was collected, and the aqueous layer was washed twice with ether. The combined organic layers were washed twice with 5% $NaHCO_3$ and once with saturated NaCl. The resulting organic material was dried, concentrated, and purified by silica gel flash chromotography[20] using 92:8 hexane/ethyl acetate. A 0.906 g (56%) sample of **5**, which gave one TLC spot, was isolated: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.2–1.6 (m, 16 H), 1.73 (t of d, 2 H, J = 7.8, 2.9 Hz), 1.93 (t, 1 H, J = 2.9 Hz), 2.18 (t of d, 2 H, J = 7.2, 2.9 Hz), 2.35 (m, 1 H), 2.6 (m, 1 H), 3.6 (br m, 1 H), 5.0–5.1 (m, 2 H), 5.65–6.0 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.0, 26.3, 28.8 (3 C), 29.1, 29.3, 29.7, 30.1, 30.2, 37.6, 37.7, 38.4, 40.2, 43.3, 68.7, 70.3, 81.3, 117.4, 136.2, 175.8; IR (NaCl disks) 3600–3200 (br, s, OH), 3300 (s, alkyne CH), 2120 (alkyne), 1720 (s, C=O), 1150 (s). Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.47; H, 10.53.

***trans*- and *cis*-2-allyl-4-(dec-9″-ynyl)-γ-butyrolactone (6a and 6b)** were prepared by refluxing 0.61 g (1.8 mmol) of **5** in 20 mL of $CDCl_3$ and 22 mg of *p*-toluensulfonic acid for 2 h[7b] (the reaction was followed by NMR). The solution was washed twice with 5% $NaHCO_3$ and once with 15% of NaCl and dried ($MgSO_4$) to give 0.456 g of crude (95%) **6a** and **6b** as an 85:15 mixture (by

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NMR integration). The oil was flash chromatographed using silica gel and 64:35:1 hexane/CH_2Cl_2/ethanol. A small sample was purified by HPLC (85:14:1 hexane/CH_2Cl_2/ethanol). **6a**: ^1H NMR ($CDCl_3$) δ 1.2–1.8 (m, 14 H), 1.94 (t, 1 H, J = 2.6 Hz) 2.0–2.1 (m, 2 H) 2.2 (t of d, 2 H, J = 2.6, 7.0 Hz) 2.2–2.4 (m, 1 H) 2.6 (m, 1 H) 2.7 (m, 1 H) 4.48 (m, 1 H, J = 5.5, 7.47 Hz) 5.1–5.2 (m, 2 H) 5.7 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.0, 25.9, 29.3, 29.6, 29.89, 29.96, 33.3, 35.5, 36.4, 39.7, 68.8, 79.55, 85.4, 118.5, 135.2, 179.5; IR (NaCl disks) 3200 (s), 2100 (m), 1770 (s), 1180 (s) cm^{-1}. The cis isomer **6b** was also present with key multiplets centered at δ 4.35 and 2.4. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.68; H, 10.09.

2-(2′,3′-Dihydroxypropyl)-4-(dec-9″-ynyl)-γ-butyrolactone (1). A mixture of 33 mg (0.28 mmol) of 4-methylmorpholine *N*-oxide monohydrate, 120 mg H_2O, and 90 μL of acetone and 18.5 mg of a 1% OsO_4 solution in *tert*-butyl alcohol, was prepared. To this, with ice-bath cooling, was slowly added 60 mg (0.23 mmol) of the **6a + 6b** mixture.[4a] After the solution was stirred 4.5 h at 0 °C, 2.3 mg of $NaHSO_3$, 28 mg of Florosil, and 0.2 mL of H_2O were added to the mixture. After filtration, the pH was adjusted to 7 with 0.5 M H_2SO_4 and the acetone was removed by rotary evaporation. The pH was then adjusted to 3 and the mixture was saturated with NaCl, extracted twice with ethyl acetate, and dried ($MgSO_4$). NMR of the product (43 mg (63%)) suggested the product was almost exclusively the desired diols 1. One of the trans isomers (relative stereochemistry 2′*S*,4*S*,2*S*), was isolated by recrystallization from CH_2Cl_2/CCl_4, mp 74–76 °C: ^1H NMR ($CDCl_3$) δ (see Table I) ^{13}C NMR ($CDCl_3$) δ 18.4, 25.3, 28.4, 28.6, 28.9, 29.2, 29.3, 33.9, 34.3, 35.3, 37.1, 66.7, 68.1, 70.6, 79.5, 84.7, 180.7; IR (NaCl disks) 3587–3337 (br m), 3300 (m), 2114 (w), 1754 (s), 1179 (m) cm^{-1}; MS (direct probe) m/e (relative intensity) 265 (17), 159 (100, M-$(CH_2)_8C{\equiv}CH$), 116 (56), 95 (61), 81 (78), 67 (94), 55 (72), 41 (89); exact mass (chemical ionization, M + 1) m/e calcd for $C_{17}H_{29}O_4$ 297.2066, found 297.2056. This MS was similar to that of rubrynolide except for the strong peak at 159 amu. The remaining isomers were characterized after acetylation and semi-preparative HPLC (see below).

2-(2′,3′-Diacetoxypropyl)-4-(dec-9″-ynyl)-γ-butyrolactone (9–12). A 15-mg sample of the synthesized isomers of 1 (the filtrate from the above crystallization) and a few crystals of DMAP were added to a dry reaction vial. Then 0.5 mL of dry CH_2Cl_2, 100 μL of Et_3N, and 70 μL of acetic anhydride were added, and the solution was stirred 2 h at room temperature. The solution was concentrated and run through a 4 × 0.3 cm plug of silica gel (30:70 ethyl acetate/hexane). The concentrated fraction containing diacetates was separated by HPLC (60:38.75:1.25 hexane/ether/ethanol).

The four acetylation products 9–12 gave two pairs of overlapping peaks at 33.6-, 34.8-, 42.4-, and 45.2-mL retention volumes, respectively, in a 2:3:4:1 ratio.[21] Heart cuts of each compound were collected and analyzed. The first and last compounds were cis lactones and the second and third were trans lactones as shown by NMR in Table III. A 50:50 mixture of rubrenolide and rubrynolide was acetylated similarly. Acetylated rubrynolide eluted at a 33.6-mL retention volume. In addition to identical HPLC retention times, acetylated rubrynolide and the first-eluting synthetic derivative gave superimposable mass, IR, ^1H and ^{13}C NMR spectra, and capillary GC column retention times (some decomposition occurred on the column). The synthetic and the natural compounds were mixed in a 3:2 ratio, and this mixture gave no new NMR peaks relative to the two separate products: ^1H NMR ($CDCl_3$) see Table III; ^{13}C NMR ($CDCl_3$) δ (lactone carbonyl too weak to observe) 19.0, 21.3, 21.5, 25.8, 25.9, 29.0, 29.3, 29.5, 29.9, 30.3, 32.7, 36.1, 36.3, 38.4, 65.7, 68.7, 69.9, 79.7, 171.16, 171.22; IR (NaCl disks) 3291 (m), 2117 (w), 1770 (s), 1743 (s), 1462 (m), 1372 (m), 1223 (s), 1043 cm^{-1}; MS m/e (relative intensity) 307 (9, M–CH_3), 201 (18), 67 (16), 55 (21), 42 (100).[1b]

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Supplementary Material Available: Details of the synthesis of 3 and 7 as well as a ^{13}C NMR spectrum of synthetic 1a (3 pages). Ordering information is given on any current masthead page.

(21) This ratio is somewhat biased since, prior to acetylation, the diol mixture was depleted of the isomer that would acetylate to give 10.

Anhydrous Hydrogen Fluoride Catalyzed Friedel–Crafts Reactions of Thioaromatic Compounds

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Sulfur-containing aromatic ketones, e.g., 4-mercaptoacetophenone[2] (1), 4-(methylthio)acetophenone[3] (**2a**), and 4′-(methylthio)-2-methylpropiophenone (**2b**), are potential intermediates for the synthesis of industrially useful compounds. 4-Mercaptoacetophenone has been used as an intermediate for the synthesis of 4-mercaptostyrene acetate[4] (4) and its polymers.[5] On the other hand, **2b** is an intermediate for the synthesis of a new UV cure photoinitiator.[6] Furthermore, 6,2-substituted naphthalenes, especially with a carbonyl substituent at the 2-position, have been found to be extremely useful in the pharmaceutical,[7] polymer,[7] and dye[8] industry.

4-Mercaptoacetophenone has been prepared from 4-hydroxyacetophenone involving Newman–Kwart rearrangement.[2] An alternate synthesis of 1 from 4-aminoacetophenone is also reported.[5] Commercially, **2b** is produced via $AlCl_3$-catalyzed Friedel–Crafts reaction of thioanisole with isobutyryl chloride.[6] Friedel–Crafts acylations for the synthesis of aromatic ketones are most commonly achieved by the use of $AlCl_3$ as a catalyst.[9] These acylations sometimes require 2 equiv of $AlCl_3$ to generate 1 mol of product. Aluminum chloride is not a

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