113. On the Funicolides, Briaranes of the Pennatulacean Coral *Funiculina quadrangularis* from the Tuscan Archipelago: Conformational Preferences in this Class of Diterpenes

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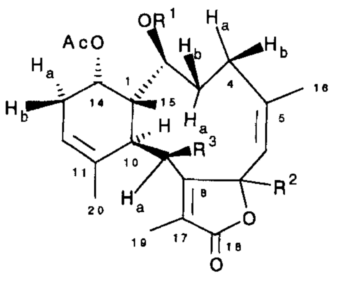
Kinetic and equilibrium NMR studies of briarane diterpenes isolated from the pennatulacean coral *Funiculina quadrangularis* showed that funicolide A (**1**), funicolide D (**5**), and brianthein W (**6**), with $R^2 = H_\beta$, undergo slow flipping by rotation of the C(1)–C(2)–C(3)–C(4) dihedral angle, giving rise to two observable conformers in a 4:96 population ratio, both having an axial AcO–C(14) and C(16) pointing 'downwards', but differing for pseudoaxial or pseudoequatorial position of R^1O, respectively. δ(C) for the minor conformers could be quickly assigned by an original emulation methodology. Similar studies revealed that funicolide B (**2**), 7-epifunicolide A (**4**), funicolide E (**7**), and unnatural epibrianthein W (**8**) undergo similar motions, where, however, the nature of the α-positioned substituent R^2 determines which conformer predominates: axial R^1O for $R^2 = H_\alpha$ (**4** and **8**) or equatorial R^1O for $R^2 = \alpha$-OH, (**2** and **7**). In contrast, funicolide C (**3**) proved to undergo slow conformational motions that involve also the cyclohexene ring, resulting in two observable conformers characterized by either an equatorial AcO–C(14) and *trans*-diaxial C(2)/C(9) or an axial AcO–C(14) and *trans*-diequatorial C(2)/C(9) in a 9:1 population ratio, respectively. These observations, and molecular-mechanics calculations for briaranes known to exhibit broad NMR signals, lead to general views on the conformational preferences of diterpenes of this class.

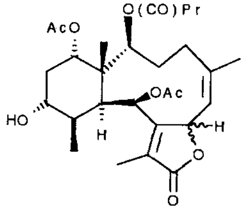
1. Introduction. – In the accompanying paper [1], we reported on a new family of briarane diterpenes, funicolides A–C (**1**–**3**), D (**5**), and E (**7**) and 7-epifunicolide A (**4**), and on the already known brianthein W (**6**) [2], isolated from the sea pen *Funiculina quadrangularis* (PALLAS, 1766) collected in the Tuscan archipelago. We also reported on unnatural 7-epibrianthein W (**8**) obtained from the base treatment of **6** [1]. We focused the attention there [1] on bis-allylic reactivity at C(7) of these 5,8(17)-diunsaturated briarane diterpenes which triggers peculiar chemical transformations leading to 16-nortaxane derivatives [1]. We noticed also broad NMR signals for these briaranes suggesting slow conformational motions, though this problem was circumvented by recording the spectra above coalescence temperature.



1 $R^1 = EtCO$, $R^2 = H_\beta$, $R^3 = H$
2 $R^1 = EtCO$, $R^2 = \alpha$-OH, $R^3 = H$
3 $R^1 = EtCO$, $R^2 = H_\beta$, $R^3 = OAc$
4 $R^1 = EtCO$, $R^2 = H_\alpha$, $R^3 = H$
5 $R^1 = PrCO$, $R^2 = H_\beta$, $R^3 = H$
6 $R^1 = Ac$, $R^2 = H_\beta$, $R^3 = H$
7 $R^1 = Ac$, $R^2 = \alpha$-OH, $R^3 = H$
8 $R^1 = Ac$, $R^2 = H_\alpha$, $R^3 = H$

We examine here the problem of broad NMR signals, which had already been noticed for other briaranes, *i.e.*, *a*) for briaranes structurally close to the funicolides due to the presence of (*Z*)–C(5)=C(6), like briareolide G (**9**) isolated from the gorgonian *Briareum* sp. [3], and verecynarmins E–G (**10**–**12**) isolated from both the sea pen *Veretillum cynomorium* and the nudibranch mollusc *Armina maculata* that feeds on it [4] (**10**–**12**, however, differ from the funicolides with respect to sp^2 hybridization at C(7)), *b*) for 5-methylidenebriaranes, like stylatulide (**13**) isolated from the sea pen *Stylatula* sp. [5], gemmacolide A (**14**) from the gorgonacean coral *Junceella gemmacea* [6], and minabein 3 (**15**) and minabein 2 (**16**) from the alcyonacean coral *Minabea* sp. [7], and *c*) for (2*E*)-2,3-unsaturated briaranes, like erythrolide B (**17**) isolated from the gorgonacean coral *Erythropodium caribaeorum* [3]. In most cases, slow conformational motions were suggested as the cause of NMR line broadening [3–7], except for **6** where small *J*(H,H) were believed to be the reason [2]. For verecynarmins B–D (**18**–**20**), studies were more accurate, albeit in a quite limited range of temperatures; two nearly equally populated conformers were observed, and it was shown that they interconvert by slow movement of the (*Z*)–C(4)=C(5) Me moiety [8]. However, we have not attempted to interpret the broad NMR signals for briareolide G (**9**), since the relative configuration at C(7) was not assigned [3].

These problems are significant in view of the various biological activities of briaranes. *E.g.*, erythrolide B (**17**) and erythrolide D have fish-deterrent activity [9] and pteroeidine



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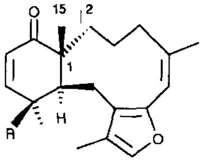
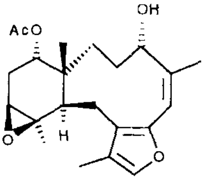


10 R=OH
11 R=H



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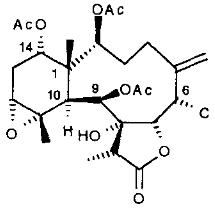

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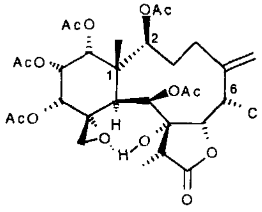

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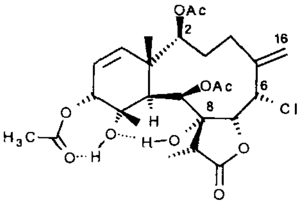

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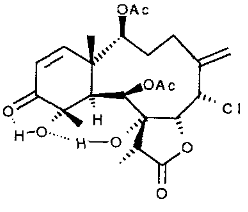

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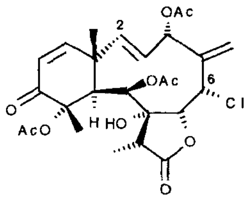

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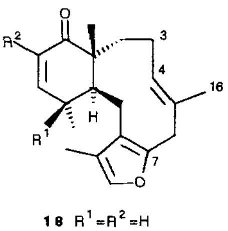

18 R^1=R^2=H
19 R^1=OH, R^2=H
20 R^1=OH, R^2=Cl

and *O*-deacetyl-9-pteroeidine are strongly ichthyotoxic [10]. Renillafoulins A–C [11] and stylatulide (**13**) [5] are potent antifouling agents. Briarein A induces chloropromazine-type CNS effects [12]. Brianthein Z, brianthein V, and brianthein Y have moderate cytotoxicity and antiviral activity [13a], and briareolides A–E [3a] and brianolide [3b] antiinflammatory effects. Finally, the solenolides [13b] inhibit rhinovirus, HSV, polio III, and Ann Arbor-, Maryland-, and Semliki-Forest viruses. This prompted us to undertake an extensive study of the conformational behavior of briaranes using dynamic NMR aided by molecular modelling. Our hope was to pave the way to unravelling the recognition phenomena where these bioactive diterpenoids are involved.

2. Results and Discussion. – 2.1. *Funicolide A* (**1**), *Funicolide D* (**5**), *and Bryanthein W* (**6**). The diterpenes **1**, **5**, and **6** can be discussed together for similarity in conformational behavior. While only signal broadening was observed by ^{1}H-NMR spectroscopy for all three compounds, two conformers, albeit at largely different relative populations, were directly detected for both **1** and **6** by ^{13}C-NMR spectroscopy at temperatures below −83°, *i.e.*, under slow-exchange conditions (*Table 1*)¹). Although on raising the temperature, the ^{13}C resonances for the minor conformer disappeared, the exchange process could be followed from ^{13}C-NMR line broadening for the major conformer ($>$ 20 Hz for the C(2), C(3), C(4), C(14), and C(16) and $<$ 10 Hz for the C(1), C(13), and C(15) signals). This suggested that conformational changes involve mainly the 'upper' portion of the molecule, as depicted in *Fig. 1*.

Molecular-mechanics (MM) calculations agreed substantially with these observations, while suggesting the involvement of three low-energy conformers: two rapidly equilibrating conformers eq-o-**1**$\rightleftarrows$eq-i-**1**²) in slow exchange with a minor conformer ax-**1** by rotation of the dihedral angle C(1)–C(2)–C(3)–C(4), while the cyclohexene ring maintains the half-chair form with an axial AcO–C(14) throughout (*Fig. 1* and *Table 2*).

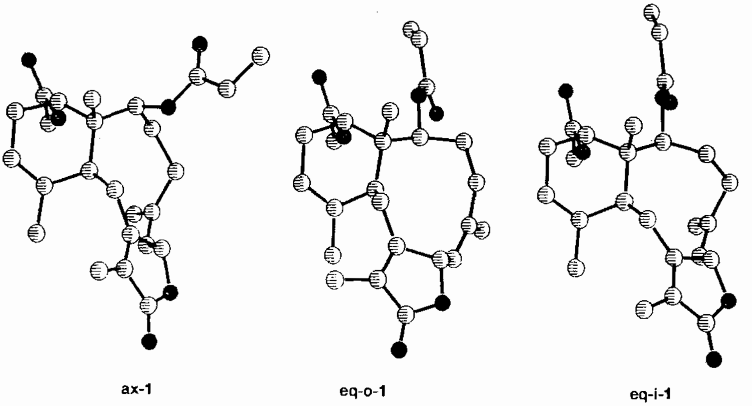

Fig. 1. *MM-Calculated lowest-energy conformers of funicolide A* (**1**)²)

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¹) For **5**, insufficient material prevented a similar study, while ^{1}H-NMR spectra were of no help due to superimposition of signals.

²) The symbols 'eq/ax' refer to the orientation of the β-positioned R^{1}O–C(2), 'i/o' to the 'inner/outer' orientation of C(16), '14ax/14eq' to the orientation of the α-positioned AcO–C(14), '6ax/6eq' to the orientation of the α-positioned Cl–C(6), 'up/down' to the position of a C-atom with respect of the near plane of the 10-membered ring, and 'crossed/parallel' to the relative spatial orientations of C(9)–C(10) and C(4)=C(5).

Table 1. *Experimentally Observed*[a]) *and Calculated*[b]) *Two-States Conformational Equilibrium for Briarane Diterpenes*[c])[d])

		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Calc.	ΔH	–2.30	–0.78	–0.53	0.14	–2.29	–2.05	–0.70	0.39	1.26	2.39	–0.61	3.74	–2.98	–1.02	0.99	0.32	0.36	0.29	0.45
	x_a/x_b	2:98	16:84	29:71	56:44	2:98	3:97	23:77	66:34	89:11	98:2	26:74	99:1	1:99	15:85	84:16	63:37	64:36	62:38	68:32
	$\Delta H^{\neq}_{ab}$	13.9	14.1	13.6	14.3	16.0	12.7	13.2	14.3	16.8	16.6	11.9	21.9	16.6	18.6	18.2	11.3	17.6	18.1	17.9
	$\Delta H^{\neq}_{ba}$	16.2	15.1	14.1	14.2	18.2	14.7	13.9	13.9	15.6	14.3	12.5	18.2	19.6	19.6	17.2	11.0	17.2	17.8	17.4
	$\Delta H^{\neq}$	13.9	14.3	13.7	14.3	16.0	12.7	13.3	13.3	15.7	14.3	12.1	18.2	16.6	18.8	17.3	11.1	17.4	17.9	17.6
Exper.	x_a/x_b	4:96	4:96	90:10	59:41	-	3:97	-	60:40									67:33	55:45	60:40
	$\Delta G^{\neq}$	15.4		14.6	13.5				13.5									17.0	17.1	17.0

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[a]) *Exper. Part.*

[b]) *Tables 2* and *3*.

[c]) Relative populations of conformers ($x_a + x_b = 1$) were calculated from *Boltzman* distribution $x_a = 1/(1 + K_{eq})$, $x_b = K_{eq}\,x_a$, where $K_{eq} = \exp(-\Delta H/(RT))$ with ΔH in J. $R = 8.31$ J/mol·K, $T = 298$ K. $\Delta H = H_b - H_a$ and $\Delta H^{\neq} = (\Delta H^{\neq}_{ab} + \Delta H^{\neq}_{ba} - (x_a - x_b)\Delta H)/2$ values are given in kcal mol^{-1}.

[d]) Subscripts 'a' and 'b' stand for conformers with a (pseudo)axial (ax) or (pseudo)equatorial (eq) group, respectively, at C(2) (at C(14) for **13**) (or for the equivalent state, considered as the sum of the populations in fast exchange according to *Boltzman* distribution among the allowed states) in the case **1**–**8** and **13**–**16**, for conformers with C(3) 'down' (3down) or 'up' (3up), respectively, in the case of **10**–**12**, for conformers with C(2) 'up' (2up) or 'down' (2down), respectively, in the case of **17**, and for the 'crossed' or 'parallel' conformations, respectively, in the case of **18**–**20**. See also *Footnote 2*.

Table 2. *MM-Calculated Lowest-Energy Conformers for Briarane Diterpenes Isolated from* F. quadrangularis (**1**–**8**) *or* V. cynomorium (**18**–**20**)[a])[2])

Dihedral angles	**1, 5, 6**[b])			**2, 4, 7, 8**		**3**[c])			**18–20**	
	ax	eq-o	eq-i	ax	eq	ax	eq-o	eq-i	crossed	parallel
C(1)–C(2)–C(3)–C(4)	*–82*	*55*	*126*	*–68*	*92*	*–55*	*55*	*126*	–79	–55
C(2)–C(3)–C(4)–C(5)	*102*	*54*	*–54*	*–56*	*–144*	*144*	*54*	*–54*	*116*	*–72*
C(3)–C(4)–C(5)–C(6)	–122	*–135*	*–65*	119	111	–107	*–132*	*–65*	*–169*	*169*
C(4)–C(5)–C(6)–C(7)	0	–1	1	0	–1	0	–1	–1	*95*	*–102*
C(5)–C(6)–C(7)–C(8)	95	90	112	–97	–86	112	93	115	*–38*	*21*
C(6)–C(7)–C(8)–C(9)	–65	–65	–69	53	61	–60	–42	–73	2	0
C(7)–C(8)–C(9)–C(10)	65	71	63	53	65	*–3*	*68*	60	80	69
C(8)–C(9)–C(10)–C(1)	–149	–146	–132	–145	–152	*–83*	*–145*	–129	–161	–155
C(9)–C(10)–C(1)–C(2)	*76*	*116*	94	69	88	*154*	*121*	96	59	56
C(10)–C(1)–C(2)–C(3)	*46*	*–78*	–62	*60*	*–60*	*–32*	*–74*	–61	49	60

[a]) In *italics* are indicated those dihedral angles that change most during the conformational motions; when three conformers are involved, the central column indicates the conformer which is in equilibrium with the other two.

[b]) The eq-o conformer is in fast exchange with the eq-i conformer or in slow exchange with the ax conformer.

The conformational movement starting from conformer ax-**1** can be described in terms of pulling C(3) towards the observer, by which R^1O changes from the pseudoaxial to the pseudoequatorial position, resulting in conformer eq-i-**1**. During this movement, a relative minimum is passed for conformer eq-o-**1**, where C(16) is only slightly turned outwards with respect to the centre of the molecule. According to these calculations, the energy difference between the average-major (eq-o$\rightleftharpoons$eq-i) and the minor conformer (ax) varies little from compound to compound, increasing only slightly in the order **6** < **5** ≈ **1**, with a high (eq-o$\rightleftharpoons$eq-i)/ax population ratio (*Table 1*).

DNMR5 Simulation for the ^{13}C-NMR signals of C(1), C(2), C(5), C(7), C(8), C(10), C(11), C(14), and C(19) of **1** allowed us to evaluate the exchange constant at the coalescence temperature for all these sites. We could thus quickly assign the C-atoms of the minor conformer (*Exper. Part*), a task which would have been difficult otherwise with so many exchange centres and low population, or much more tedious (*e.g.* assignment by our cross-saturation transfer methodology [14]). The kinetic parameters calculated from the equation $\ln(k/T) = f(1/T)$ were in excellent agreement with the experimental observations (*Table 1*). The proposed average-major conformer eq-o$\rightleftharpoons$eq-i (*Fig. 1*) is also supported by NOE effects [1][3]).

2.2. *Funicolide B* (**2**), *7-Epifunicolide A* (**4**), *Funicolide E* (**7**), *and 7-Epibrianthein W* (**8**). The diterpenes **2**, **4**, **7**, **8** showed broad ^{1}H-NMR signals at room temperature. On lowering the temperature to < –73°, two conformers in slow exchange in a 3:2 population ratio for both **4** and **8** could be directly detected by ^{1}H-NMR, while lowering of the temperature down to –85° was needed to observe by ^{13}C-NMR two conformers for compound **2** in a 4:96 population ratio (*Table 1*). Insufficient material prevented similar studies for **7**.

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[3]) Interpretation of broad ^{1}H-NMR signals for brianthein W (**6**) as due to small couplings [2] has, therefore, to be abandoned.

MM Calculations for these briaranes suggested, as for the briaranes **1**, **5**, and **6** (see above), that motions related to rotation of the dihedral angle C(1)–C(2)–C(3)–C(4) are responsible for the observed NMR-signal broadening, with the involvement of only two low-energy conformers, however (*Fig. 2* and *Table 2*): a major conformer (ax for **4** and **8** or eq for **2** and **7**[2])) and a minor conformer (eq for **4** and **8** or ax for **2** and **7**[2])). According to these calculations, both the remaining portion of the ten-membered cycle and the six-membered cycle change little during the interconversion of the conformers, which differ in energy by 0.14 and 0.39 kcal mol^{-1} for **4** and **8**, respectively, corresponding to ax/eq population ratios 56:44 and 2:1 (*Table 1*). For **2**, conformer eq-**2** was calculated to be more stable than ax-**2** by 0.8 kcal mol^{-1}, corresponding to a ax/eq population ratio 1:5 (*Table 1*). This analysis suggested that steric repulsions between the α-positioned OH–C(7) and both H_a–C(4) and H–C(10) are at the origin of the higher energy of conformers ax-**2** and ax-**7**.

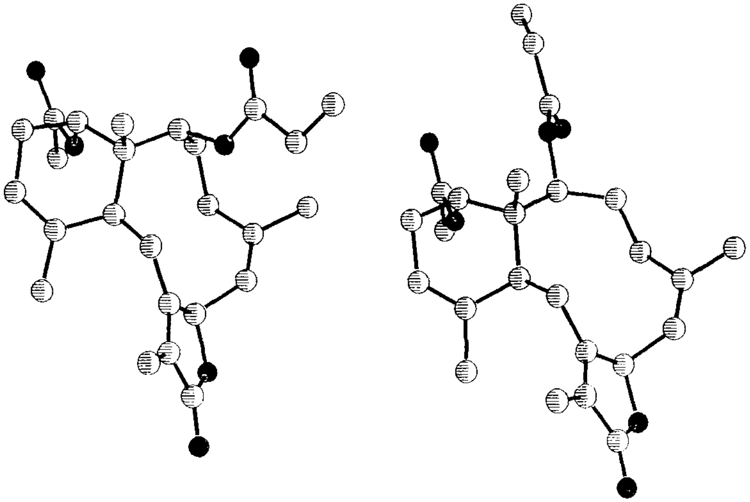


Fig. 2. *MM-Calculated lowest-energy conformers of 7-epifunicolide A* (**4**)[2])

DNMR5 Simulations for the H–C(7) signal in a wide range of temperatures allowed us to evaluate the coalescence temperature and the kinetic parameters for compounds **4** (*Fig. 3*) and **8** (*Table 1*).

2.3. *Funicolide C* (**3**). All ^{1}H-NMR signals for funicolide C (**3**) were sharp at temperatures > *ca.* 60°, while on cooling to 20° broadening of the signals for H–C(2), 2 H–C(3), H–C(7), 2 H–C(13), and H–C(14) was observed, and on further cooling to –70° two conformers showed up in a 9:1 population ratio (*Table 1*). The spatial positions of the equatorial and axial AcO–C(14) in the major (ax-**3**[2])) and minor conformer eq-**3**[2]), respectively, were assigned from cross-saturation transfer experiments [14] (irradiation at

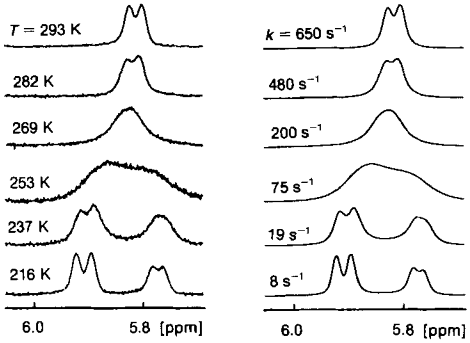
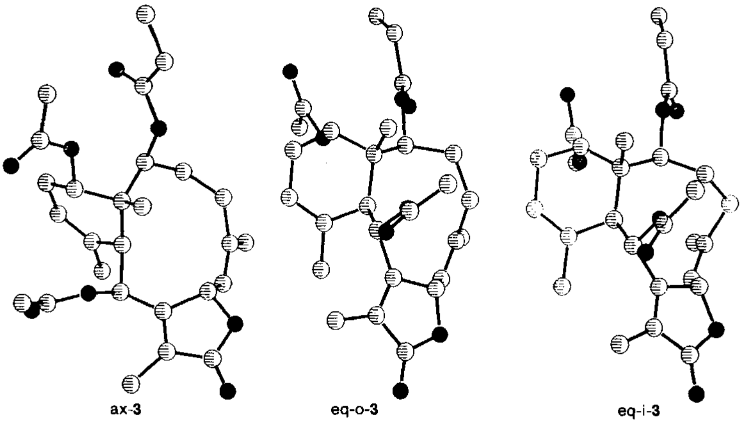


Fig. 3. *Experimental* (left) *and DNMR5-calculated* (right) *^{1}H-NMR line shape for the H–C(7) signal of equilibrium conformers ax-***4** *and eq-***4** *of 7-epifunicolide A*

δ 4.70 (br. *s*) of the minor eq-**3**→intensity decrease at δ 4.98 (br. *t*) for H–C(14) of the major ax-**3**)[4]).

In accordance with the above experimental observations, MM calculations for **3** suggested that two rapidly equilibrating minor conformers eq-o-**3** and eq-i-**3**, both having an axial AcO–C(14), are involved in slow exchange with the dominant conformer ax-**3**, which unusually has an equatorial AcO–C(14) and C(2) and C(9) in *trans*-diaxial position (*Fig. 4* and *Table 2*). Kinetic data, derived from DNMR5 simulation for the H–C(14) signal of **3**, are shown in *Table 1*. It should be noticed that in this case, there is lack of quantitative agreement between the experimental observations and MM calculations which underestimate the contribution of the unusual conformer ax-**3**. This might



ax-**3** eq-o-**3** eq-i-**3**

Fig. 4. *MM-Calculated lowest-energy conformers of funicolide C* (**3**)[2])

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[4]) In this context it is important to note that briaranes isolated from the gorgonian *Solenopodium excavatum* [15] were found to exist exclusively in the unusual conformation characterized by an equatorial AcO–C(14), corresponding to a C(9)–C(10)–(1)–C(2) dihedral angle of *ca.* 155°.

reflect our difficulties (not solved, even not by using a global, steric-energy-minimization search) in locating other conformers in fast exchange with ax-**3**.

2.4. *A Comparative Examination of Known Briaranes with Broad NMR Signals.* We also carried out MM calculations for briaranes that were described in the literature to show broad NMR signals. Included are verecynarmin E–G (**10**–**12**) [4], minabein 3 and 2 (**15** and **16**), respectively [7], and erythrolide B (**17**) [3] which reportedly showed broad signals for all H- and C-atoms at room temperature, with signal sharpening on raising the temperature to 45–60°. We took also into account stylatulide (**13**) [5] and gemmacolide (**14**) [6] which were shown to exhibit broad H–C(6)/C(6) and H–C(7)/C(7) signals at room temperature with signal sharpening at 50–60°. Because of unassigned configuration at C(7) [3a], briareolide G (**9**) was discarded, regrettably because of its most close structural relationship to funicolide C (**3**).

Our MM calculations (*Tables 1* and *3*) suggest the following interpretations. *i*) For compounds **10**–**12**, slow interconversion between 3down and 3up conformers2) involves rotation of the dihedral angle C(1)–C(2)–C(3)–C(4); for both **10** and **11**, the minor 3up conformer has C(3) 'upwards', which thus experiences 1,3-steric repulsions with Me(15), while for **12** the minor 3down conformer has C(3) 'downwards'. *ii*) For **13**, in contrast, the main slow conformational motion involves rotation of the AcO–C(14)–C(1)–C(10) dihedral angle (14ax-**13**$\rightleftharpoons$14eq-**13**2)); the dominant (99%) conformer 14ax-**13** is characterized by (pseudo)axial positions of both AcO–C(14) and Cl–C(6), which are both inverted to (pseudo)equatorial positions in the minor (1%) conformer 14eq-**13**. *iii*) The major conformer of gemmacolide, eq-**14**2), takes a shape similar to the major conformer of **13**, while the minor conformer ax-**14**, where H-bonding is involved (see *Formula*), is

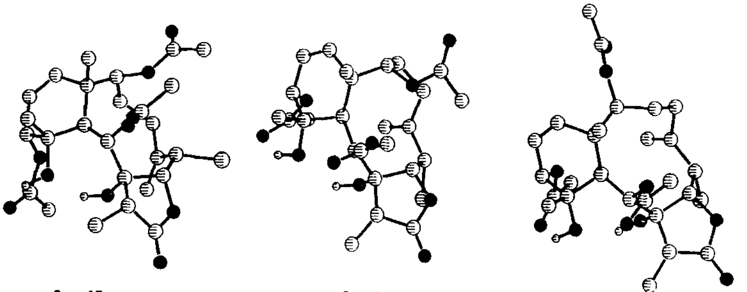
Table 3. *MM-Calculated Lowest-Energy Conformers of Briarane Diterpenes* **10**–**17** *Isolated from Various Pennatulacean Corals*a)2)

Dihedral angles	**10**–**12**		**13**		**14**		**15**, **16**b)			**17**c)		
	3down	3up	14ax	14eq	ax	eq	ax,eq	ax,6ax	eq,6ax	2up, 6ax	2up, 6eq	2down, 6eq
C(1)–C(2)–C(3)–C(4)	*–83*	*79*	*153*	*105*	*–70*	*153*	–119	*–110*	*133*	–172	*–172*	*171*
C(2)–C(3)–C(4)–C(5)	*109*	*31*	–73	–73	*87*	*–72*	78	*85*	*–67*	110	*91*	*–82*
C(3)–C(4)–C(5)–C(6)	–124	–119	–58	–69	*–156*	*–59*	*–90*	*–126*	*–88*	–90	–69	–45
C(4)–C(5)–C(6)–C(7)	2	0	*124*	*86*	*66*	*124*	*139*	*79*	70	*64*	*122*	121
C(5)–C(6)–C(7)–C(8)	51	50	*–43*	*64*	*54*	*–44*	*–44*	*63*	65	*57*	*–50*	*–48*
C(6)–C(7)–C(8)–C(9)	–1	2	–75	–97	–89	–75	*–64*	*–109*	–105	*–140*	*–78*	*–78*
C(7)–C(8)–C(9)–C(10)	30	43	142	45	100	142	104	77	92	97	121	138
C(8)–C(9)–C(10)–C(1)	–145	–144	–86	–107	–147	–87	–131	–123	–125	–89	–100	–87
C(9)–C(10)–C(1)–C(2)	58	85	*45*	*135*	59	45	79	77	89	49	49	52
C(10)–C(1)–C(2)–C(3)	*57*	*–69*	–84	–74	*46*	*–85*	51	*60*	*–67*	65	*63*	*–103*

a) In *italics* are indicated those dihedral angles that change most during the conformational motions; when three conformers are involved, the central column indicates the conformer which is in equilibrium with the other two.

b) The ax,6ax conformer is in fast exchange with the ax,6eq conformer or in slow exchange with the eq,6ax conformer.

c) The 2up,6eq conformer is in fast exchange with the 2up,6ax conformer or in slow exchange with the 2down,6eq conformer.



ax,6eq-**15** ax,6ax-**15** eq,6ax-**15**

Fig. 5. *MM-Calculated lowest-energy conformers of minabein 3* (**15**)[2])

obtained by rotation of the C(1)–C(2)–C(3)–C(4) dihedral angle and has a pseudoaxial AcO–C(2) (during this conformational movement, Cl–C(6) changes from pseudoaxial to pseudoequatorial). *iv*) There are three relevant conformers for compounds **15**–**17** (*Fig. 5* and *Tables 1* and *3*), all, except **17**, stabilized by H-bonding (see *Formulae*); the medium-populated conformer ax,6ax-**15**[2]) for minabein 3, having both AcO–C(2) and Cl–C(6) in pseudoaxial positions and C(16) pointing downwards, is interconverted with either the major conformer eq,6ax-**15** (AcO–C(2) pseudoequatorial) by slow rotation of the C(1)–C(2)–C(3)–C(4) dihedral angle or with the minor conformer ax,6eq-**15** (Cl–C(6) pseudoequatorial) by fast rotation of the dihedral angle C(5)–C(6)–C(7)–C(8). Analogous motions are suggested for minabein 2, where, however, the major conformer ax,6ax-**16** interconverts slowly with the medium-populated conformer eq,6ax-**16** and rapidly with the minor conformer ax,6eq-**16**. For erythrolide B, the major conformer 2up,6eq-**17** is in slow exchange with the medium-populated conformer 2down,6eq-**17** and in fast exchange with the minor conformer 2up,6ax-**17**. In this case, the slow exchange process could not be simulated through a single dihedral angle. Interconversion between the two forms could, however, be obtained by simultaneous rotations of the dihedral angles C(2)–C(3)–C(4)–C(5) (*e.g.*, from +90° to −80°, by steps of −10°) and C(1)–C(2)–C(3)–C(4) (*e.g.*, from −170° to +170°, by steps of −5°).

For verecynarmins B–D (**18**–**20**), similar calculations suggested that the major and the minor conformer take the 'crossed' and the 'parallel' form [8], respectively (*Table 2*), in agreement with NMR data [8]. Conformational interconversion between these two forms was achieved through simultaneous rotations of the dihedral angles C(4)–C(5)–C(6)–C(7) (*e.g.*, from +90 to −100°, by steps of −10°) and C(3)–C(4)–C(5)–C(6) (*e.g.*, from −170 to +170°, by steps of −5°). DNMR5 Simulation of the 3 H–C(16) signal led to the kinetic parameters listed in *Table 1*, which show that interconversion barriers had been underestimated by our previous rough calculations [8].

3. Conclusions. – This work showed that slow conformational motions in briarane diterpenes usually involve only the ten-membered ring, though in particular cases also the six-membered ring may participate.

Four types of motions were identified for the ten-membered ring. *1*) Slow rotation of the dihedral angle C(1)–C(2)–C(3)–C(4) resulting in C(2) 'up'/C(3) 'down'[2]) position, *i.e.*, the β-group at C(2) is pseudoaxial, or in C(2) 'down'/C(3) 'up' position, *i.e.*, the β-group at C(2) is pseudoequatorial. Change of the β-substituent at C(2) may affect the populations of the conformers. This is the most frequently encountered conformational situation for briaranes, applying to compounds **1**–**8**, **10**–**12**, **14**–**16**. *2*) In case of a (*Z*)–C(5)=C(6) bond, as in compounds **1**–**8** and **10**–**12**, MM calculations suggest that there is also a 'fast flipping out/flipping in' motion of C(16). *3*) In case of both C(5)=C(16) and Cl_α–C(6), as in compounds **13**–**17**, motions deriving from 'fast' rotation of the dihedral angle C(5)–C(6)–C(7)–C(8) occur, and the conformers are characterized by either a pseudoaxial or a pseudoequatorial Cl-atom. *4*) In the presence of a (*E*)-C=C bond in the ten-membered ring, such as in compounds **17**–**20**, simultaneous, slow motions from cooperative rotation of two dihedral angles determine the overall conformational process.

Chair-chair inversion of the six-membered ring occurs in compounds **3** and **13**, resulting in the unusual conformation characterized by an equatorial AcO–C(14) and C(2) and C(9) in *trans*-diaxial position, which is dominant for **3** or minor for **13**. In a study of the solenolides, it was concluded that β-ester groups at C(2), C(3), and C(13) are required for the adoption of this unusual conformation [15]. Our experimental observations for funicolide C (**3**) and calculations for **13** suggest that there may be other combinations of structural elements forcing briaranes into this unusual conformation, which becomes sizeably populated to relieve repulsive interactions between β-ester groups at C(2) and C(9). Probably this unusual conformation of briaranes comes into play whenever there are strong repulsive interactions between bulky β-substituents at the ten-membered ring.

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Experimental Part

1. *General*. See [1] [8]. Molecular mechanics (MM) calculations were carried out with the PCMODEL 4.0 computer program, setting the dielectric constant to $\varepsilon = 1.5$. Global, steric-energy-minimization search was carried out with the GLOBAL-MMX (GMMX) computer program. Both programs are based on the MMX force field from *Serena Software*, Bloomington, Indiana [16]. NMR Line-shape simulation (*Fig. 3*) was carried out with the computer program DNMR5 [17]. NMR: *Varian XL-300*, ^{1}H at 299.94 MHz and ^{13}C at 75.43 MHz in $CDCl_3$ at the indicated temp.; selected ^{13}C-NMR data are reported, *i.e.*, δ of the major conformer in ppm (values in italics in parentheses refer to the minor conformer) the signal multiplicity, $w_{1/2}$(max) in Hz at the indicated temp., and C-atom; selected ^{1}H-NMR data are also reported, with data for the minor conformer in italics in parentheses; saturation transfer was obtained with 6 s of pre-irradiation.

2. *Funicolide A* (*= (+)-(1*R*,2*R*,7*R*,10*R*,14*R*,5*Z*)-14-Acetoxy-18-oxobriara-5,8(17),11-trien-2-yl Propanoate = (+)-(3a*R*,8*R*,8a*R*,9*R*,12a*R*,4*Z*)-9-Acetoxy-2,3a,6,7,8,8a,9,10,12a,13-decahydro-1,5,8a,12-tetramethyl-2-oxobenzo[4,5]cyclodeca[1,2-*b*]furan-8-yl Propanoate*; **1**). ^{13}C-NMR (−85°): 40.65 (*42.40*) (*s*, $w_{1/2}$ = 10.2 (30°), C(1)); 73.61 (*60.55*) (*d*, $w_{1/2}$ = 35 (40°), C(2)); 32.95 (*t*, $w_{1/2}$ = 42.0 (40°), C(3)); 28.90 (*t*, $w_{1/2}$ = 8.8 (15°) C(4)); 143.94 (*142.11*) (*s*, $w_{1/2}$ = 11.4 (30°), C(5)); 121.62 (*121.99*) (*d*, $w_{1/2}$ = 3.4 (9°), C(6)); 80.91 (*80.38*) (*d*, $w_{1/2}$ = 4.0 (9°), C(7)); 160.16 (*161.02*) (*s*, $w_{1/2}$ = 6.2 (20°), C(8)); 28.90 (*t*, $w_{1/2}$ = 8.8 (15°), C(9)); 36.87 (*35.89*) (*d*, $w_{1/2}$ = 7.0 (20°), C(10)); 135.66 (*135.38*) (*s*, $w_{1/2}$ = 3.3 (9°), C(11)); 116.41 (*116.68*) (*d*, $w_{1/2}$ = 3.8 (9°), C(12)); 25.64 (*t*, $w_{1/2}$ = 16.4 (30°), C(13)); 72.00 (*81.40*) (*d*, $w_{1/2}$ = 25.0 (40°), C(14)); 14.61 (*16.02*) (*q*, $w_{1/2}$ = 11.2 (30°), C(15)); 26.98 (*q*, $w_{1/2}$ = 30.0 (40°), C(16)); 124.12 (*123.00*) (*s*, $w_{1/2}$ = 6.9 (20°), C(17)); 174.45 or 174.60 (*s*, $w_{1/2}$(max) not detected, C(18)); 9.77 (*9.66*) (*q*, $w_{1/2}$ = 2.2 (2°), C(19)); 21.50 (*q*, $w_{1/2}$ = 6.5 (20°), C(20)); 8.59 (*9.05*) (*q*, $w_{1/2}$ = 3.7 (9°), *Me*CH_2CO–C(2)); 27.80 (*t*, $w_{1/2}$ = 2.8 (2°), Me*C*H_2CO–C(2)); 174.60 or 174.45 (*s*, MeCH_2*C*O–C(2)); 21.33 (*q*, $w_{1/2}$ = 4.8 (15°), *Me*CO–C(14)); 171.21 (*q*, $w_{1/2}$ = 4.9 (20°), Me*C*O–C(14)).

3. *Funicolide C* (*= (+)-(1*R*,2*R*,7*R*,9*R*,10*R*,14*R*,5*Z*)-9,14-Diacetoxy-18-oxobriara-5,8(17),11-trien-2-yl Propanoate = (+)-(3a*R*,8*R*,8a*R*,9*R*,12a*R*,13*R*,4*Z*)-9,13-Diacetoxy-2,3a,6,7,8,8a,9,10,12a,13-*

decahydro-1,5,8a,12-tetramethyl-2-oxobenzo[4,5]cyclodeca[1,2-b]furan-8-yl Propanoate; **3**). ^{1}H-NMR ($CDCl_3$, −75°): 5.40 (*5.32*) (br. *s*, H−C(2)); 5.17 (*5.10*) (br. *d*, *J*(6,7) = 9.6, H−C(6)); 6.18 (*5.63*) (br. *d*, *J*(7,6) = 9.5, H−C(7)); 6.42 (*6.42*) (br. *s*, H_a−C(9)); 3.40 (*3.00*) (br. *s*, H−C(10)); 5.40 (*4.85*) (br. *s*, H−C(12)); 4.98 (br. *t*, *J* = 8.0, H−C(14)), (*4.70* (*br. s*)); 1.39 (*1.04*) (br. *s*, 3 H−C(15)); 1.76 (br. *s*, 3 H−C(16)); 1.81 (br. *s*, 3 H−C(19)); 1.66 (br. *s*, 3 H−C(20)); 2.00 (*s*, AcO); 1.13 (*t*, *J* = 7.5, *Me*CH_2CO).

4. _7-Epifunicolide A (= (−)-(1R*,2R*,7S*,10R*,14R*,5Z)-14-Acetoxy-18-oxobriara-5,8(17),11-trien-2-yl Propanoate = (−)-(3aR*,8S*,8aS*,9S*,12aS*,4Z)-9-Acetoxy-2,3a,6,7,8,8a,9,10,12a,13-decahydro-1,5,8a,12-tetramethyl-2-oxobenzo[4,5]cyclodeca[1,2-b]furan-8-yl Propanoate_; **4**). ^{1}H-NMR (−96°): 4.92 (br. *s*, H−C(2)); 4.84 (br. *d*, *J*(6,7) = 7.0, H−C(6)), (*4.77* (br. *d*, *J* = 5.5)); 5.92 (br. *d*, *J*(7,6) = 8.0, H−C(7)), (*5.78* (br. *d*, *J* = 5.5)); 4.68 (br. *s*, H−C(14)); 0.81 (*1.04*) (br. *s*. 3 H−C(15)); 1.67 (br. *s*, 3 H−C(16)); 1.85 (br. *s*, 3 H−C(19)); 1.52 (*1.48*) (br. *s*, 3 H−C(20)); 2.10 (*2.08*) (*s*, AcO); 1.09 (*1.08*) (*t*, *J* = 7.5, *Me*CH_2CO).

5. _Brianthein W (= (+)-(1R*,2R*,7R*,10R*,14R*,5Z)-18-Oxobriara-5,8(17),11-triene-2,14-diyl Diacetate = (+)-(3aR*,8R*,8aR*,9R*,12aR*,4Z)-2,3a,6,7,8,8a,9,10,12a,13-Decahydro-1,5,8a,12-tetramethyl-2-oxobenzo[4,5]cyclodeca[1,2-b]furan-8,9-diyl Diacetate_; **6**). ^{13}C-NMR (−85°): 40.57 (*42.35*) (*s*, $w_{1/2}$ = 12.2 (30°), C(1)); 73.75 (*d*, $w_{1/2}$ = 34.7 (37°), C(2)); 32.91 (*t*, $w_{1/2}$ = 33.0 (37°), C(3)); 28.88 or 28.82 (*t*, $w_{1/2}$ = 29.3 (40°), C(4)); 143.92 (*142.05*) (*s*, $w_{1/2}$ = 11.3 (30°), C(5)); 121.43 (*121.84*) (*d*, $w_{1/2}$ = 2.8 (10°), C(6)); 80.93 (*80.64*) (*d*, $w_{1/2}$ = 3.5 (10°), C(7)); 160.15 (*161.05*) (*s*, $w_{1/2}$ = 6.7 (22°), C(8)); 28.82 or 28.88 (*t*, $w_{1/2}$ = 9.0 (20°), C(9)); 36.87 (*35.92*) (*d*, $w_{1/2}$ = 6.2 (25°), C(10)); 135.99 (*135.36*) (*s*, $w_{1/2}$ = 3.0 (10°), C(11)); 116.44 (*116.73*) (*d*, $w_{1/2}$ = 3.5 (10°) C(12)); 26.53 (*t*, $w_{1/2}$ = 19.8 (35°), C(13)); 71.90 (*81.46*) (*d*, $w_{1/2}$ = 30.0 (35°), C(14)); 15.54 (*16.01*) (*q*, $w_{1/2}$ = 10.7 (23°), C(15)); 27.70 (*q*, $w_{1/2}$ = 27.1 (44°), C(16)); 124.15 (*123.03*) (*s*, $w_{1/2}$ = 7.5 (22°), C(17)); 174.64 (*s*, $w_{1/2}$ = 4.4 (17°), C(18)); 9.79 (*9.55*) (*q*, $w_{1/2}$ = 3.5 (10°), C(19)); 21.49 (*q*, $w_{1/2}$ = 6.4 (22°), C(20)); 21,36, 21.16 (2*q*, 2 *Me*CO); 171.39, 171.12 (2*s*, 2 Me*C*O).

6. _7-Epibrianthein W (= (−)-(1R*,2R*,7S*,10R*,14R*,5Z)-18-Oxobriara-5,8(17),11-triene-2,14-diyl Diacetate = (−)-(3aR*,8S*,8aS*,9S*,12aS*,4Z)-2,3a,6,7,8,8a,9,10,12a,13-Decahydro-1,5,8a,12-tetramethyl-2-oxobenzo[4,5]cyclodeca[1,2-b]furan-8,9-diyl Diacetate_; **8**). ^{1}H-NMR (−75°): 4.94 (*m*, H−C(2)); 3.06 (br. *t*, *J* = 13.0, H_a−C(4)); 4.86 (br. *d*, *J* = 7.8, H−C(6)), (*4.78* (br. *d*, *J* = 5.7)); 5.92 (br. *d*, *J*(7,6) = 8.4, H−C(7)), (*5.77* (br. *d*, *J* = 5.7)); 3.21 (br. *d*, *J* = 16.0 H−C(9)); 3.28 (br. *d*, *J* = 9.0, H−C(10)); 5.21 (br. *s*, H−C(12)), (*5.27* (*J*(12,13) = 5.1)); 4.69 (br. *s*, H−C(14)); 0.83 (*1.03*) (br. *s*, 3 H−C(15)); 1.70 (*1.67*) (br. *s*, 3 H−C(16)); 1.86 (*1.85*) (br. *s*, 3 H−C(19)); 1.53 (*1.49*) (br. *s*, 3 H−C(20)); 2.03, 2.06 (2*s*, 2 AcO).

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