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ON TOPOGRAPHY AND FUNCTIONALITY IN THE B-D RINGS OF CEPHALOSTATIN CYTOTOXINS

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Abstract: Analogues 12'β-hydroxycephalostatin 1 (**9**), 7'-deoxyritterazine G (**10**), and 14-*epi*-7'-deoxyritterazine B (**11**) were prepared via our protocol for unsymmetrical pyrazine synthesis. Cytotoxicity against human tumors was also determined for the first time for ritterazines, with *femtomolar potency* and a high correlation to cephalostatins observed. The SAR of these and related compounds provide insight into the importance of topography and certain chemical functionality in the B-D and B'-D' rings of cephalostatin type antineoplastics.

Introduction[1]

The cephalostatins[2] and ritterazines[3] comprise a growing family of forty-five bis-steroidal marine products displaying extreme cytotoxicity (fM-nM ED_{50} vs P388). In addition to subnanomolar *in vitro* activity in the NCI-60 human tumor panel, cephalostatins have shown promise *in vivo* against murine leukemia and brain tumor xenografts.[2b] All 19 cephalostatins appear to act by the same unknown, possibly novel mechanism as indicated by high correlations of their characteristic NCI screening profiles.[2] Whether the structurally related ritterazines would show similar potency or mechanism against human cancer was unknown. Cephalostatins 1 (**1**), 7 (**2**) and ritterazine G **3** are of particular interest since they feature the four most active basic steroidal subunit types of the six which describe the entire family.[4] We recently reported the first total syntheses of **1** and its analogue ritterostatin G_N1_N **4**,[4,5] and previously that of **2** and ritterazine K **8** (Figs. 1 and 4).[6] Questions unanswered by the natural series or previous analogues include roles of the C/D ring functionality arrays and oxidation states at C7' and C12. We therefore desired synthetic compounds which might further define relevant parameters for the lower (B–D, B'–D'), non-spiroketal rings of cephalostatin-type antitumor agents.

Since the "interphylal" hybrid **4** composed of the North hemispheres of **1** (North 1)[7] and **3** (North G)[4] was highly potent (GI_{50} 14 nM), the cytotoxicities of analogues derived from coupling these units to select South units were expected to provide significant insights. Ritterazine B **5** (14βH,22β), closely related to ritterazines G **3** (Δ^{14},22α) and F **6** (14βH,22α), is the most potent of the ritterazines discovered (Figs. 1 and 4).[3] We therefore included 14α-North B as a third upper hemisphere for study based on the excellent potency of the 14'αH (i.e. 14'α,15'-dihydro) analogue **7** (GI_{50} 2.4 nM) of **1** (GI_{50} 1.2 nM).[8]

The South 7 unit[9a,b] seemed a logical constant for exploring variations in the Northern partners and for direct comparison to the 7'OH-South 7 unit, common to many ritterazines but absent from all cephalostatins. Ritterazine K **8**, the dimer of South 7, and ritterazine B **5** were also tested for the first time against human tumor cells to permit direct comparison of cytotoxicity. Finally, to explore the influence on potency reported for oxidation of the 12βOH of **5** (Fig. 4),[3] we wished to reduce the 12'ketone of the South 1 unit of **1**. Thus, analogues **9**, **10**, and **11** (Fig. 1) were designed with these appropriately modified steroid units.

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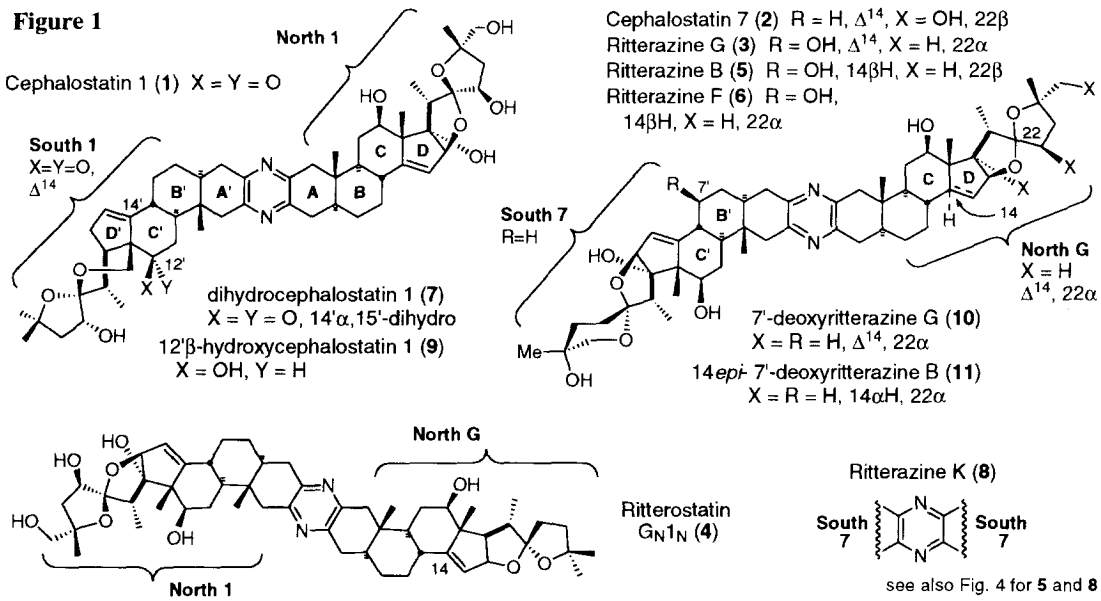
Figure 1



Synthesis of Cephalostatin and Ritterazine Analogues

Preparation of 14-*epi*-North B was readily achieved from the known 14αH-17-deoxy-North 1 model (**12**, Fig. 2).[9c,d] Desilylation and subjection to a Barton bisdeoxygenation sequence[10] gave **13**.[11] Selective hydrolysis of the 3β-acetate followed by oxidation furnished 14-*epi*-North B as the 3-ketone **14**.

The analogues 12β-hydroxycephalostatin 1 (**9**), ritterostatin G_N7_S (**10** = 7'-deoxyritterazine G) and 14*epi*-7'-deoxyritterazine B (**11**), were prepared via our protocol for unsymmetric pyrazine synthesis from the appropriate azidoketones and aminomethoximes (Fig. 3 and Table 1). These coupling partners were derived from the corresponding 3-ketones in the usual manner.[4,7–9] For **9**, Luche reduction[12] (99%) of the 12'-ketone in the initial pyrazine coupling product (masked cephalostatin 1)[4] preceeded routine deprotection to afford **9**.

Figure 2

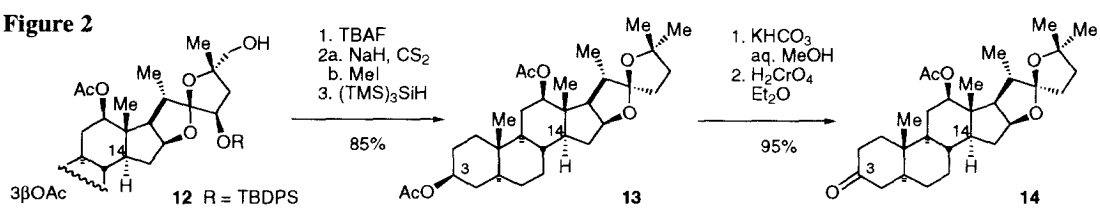


Figure 3

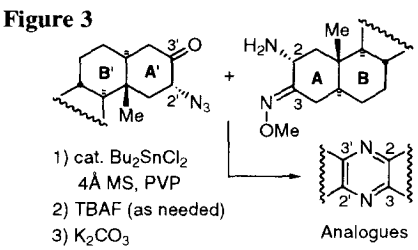


Table 1. Yields for derivation of coupling partners from 3-ketosteroids, pyrazine formation, and deprotection.[11]

Azidoketone	Aminomethoxime	Pyrazine	Analogue
South 1 (68%)[4]	North 1 (57%)[4,7]	59%	**9** (84%)
South 7 (65%)[9]	North G (63%)[4]	60%	**10** (80%)
14*epi*-North B (56%)	South 7 (55%)[9]	50%	**11** (70%)

Table 2. Cytotoxicities against representative human tumor cell lines in the PCCL panel (ED_{50} nM, 6 day exposure).[13]

Compound	Lung A-549	Breast avg 1–3 types	Colon HT-29	Renal A-498	Prostate PC-3	Bladder PACA-2	PCCL avg. (6-8 lines)	(ref) P388
Adriamycin	6.2	150	37	3.5	57	6.3	18.7	-
ritterazine K (**8**)[6]	$3.7x10^{-4}$	11	28	$8.4x10^{-4}$	0.0021	0.051	0.047	(3) 10
cephalostatin 7 (**2**)[6]	$3.0x10^{-5}$	38	30	$5.5x10^{-4}$	0.0021	0.41	0.052	(2) 10^{-4}–10^{-6}
7'deoxy-ritterazine G (**10**)	$1.5x10^{-5}$	0.036	0.012	$1.6x10^{-5}$	$1.8x10^{-4}$	$7.2x10^{-4}$	$3.3x10^{-4}$	-
ritterazine B (**5**)[3]	$2.8x10^{-6}$	0.0021	$4.6x10^{-4}$	$1.2x10^{-6}$	$1.8x10^{-5}$	$5.2x10^{-6}$	$2.6x10^{-5}$	(3) 0.17
12OH-cephalostatin 1 (**9**)	$2.4x10^{-5}$	0.0011	0.0012	$3.5x10^{-5}$	$1.3x10^{-4}$	$1.7x10^{-4}$	$1.5x10^{-4}$	-
dihydrocephalostatin 1 (**7**)[8]	$2.4x10^{-6}$	$2.2x10^{-5}$	$3.0x10^{-4}$	$9.7x10^{-6}$	$2.9x10^{-5}$	$8.6x10^{-5}$	$2.7x10^{-5}$	-
cephalostatin 1 (**1**)[4]	$1.5x10^{-6}$	$2.8x10^{-4}$	$2.1x10^{-4}$	$5.0x10^{-6}$	$2.3x10^{-5}$	$1.7x10^{-5}$	$2.4x10^{-5}$	(2) 10^{-4}–10^{-6}

Antitumor Activity and Structure Analysis

In vitro cytotoxicity data against human tumors for the analogues and related compounds is summarized in Tables 2 and 3. Purdue Cell Culture Laboratory (PCCL, Table 2, ED_{50}, 6 d exposure)[13] and National Cancer Institute (NCI, Table 3, GI_{50}, 48 h exposure)[14] values are not intended to be directly comparable, although the terms ED_{50} and GI_{50} describe the same 50% growth inhibition of cultured tumors. They do indicate similar trends (note entries for **1–2**, **5**, **8–10** in each Table) and a very strong time-dependence of cytotoxicity.[15]

The analogue and natural product pyrazines consistently showed much lower ED_{50}'s than the standard chemotherapeutic adriamycin. Remarkably, the cytotoxicities of ritterazine B (**5**) and cephalostatin 1 (**1**) are essentially indistinguishable (Tables 2 and 3). COMPARE[14a] pattern-recognition analyses gave correlation coefficients of 0.93 and 0.85 for **5** and **8**, respectively, in reference to **1**, implying that the cytotoxic mechanism of the ritterazines does not diverge substantially from that of the cephalostatins. These tests provide the first evidence that the high activity displayed by ritterazines against P388 are reflected by extreme potencies against human cancer cells. Table 2 further shows that extended exposure of natural and analogue bissteroids to tumors result in *femtomolar activity*. Suggestion of extreme potency has been observed in the NCI tests of **1**; **5** and other ritterazines are currently being further evaluated under that protocol.

As no correlation of *in vitro* to *in vivo* potency has been made, the SAR indications must be considered preliminary. Likewise, since the overall topography and functionality of **1** and **5** initially appear so different, a specific rationale for their similar potencies would be premature. Some relationships, however, appear evident.

Table 3. Cytotoxicities vs representative tissue types in the NCI-60 panel (GI_{50} nM, 2 day exposure), 60-line avg., % of cell lines affected,[14a–d] and avg. GI_{50} in a subset of 10 lines (NCI-10) characteristically sensitive to this class of compounds.[14e]

		Leukemia	Lung	Colon	CNS	Breast	Ovary	Skin	Renal		Prostate	**avg.**	**avg.**
Cpd	Partner subunits	HL -60	A-549	HT -29	SF-295	MCF -7	IGR OV1	LOX IMVI	A-498	RXF -393	PC -3	NCI-60 (%lines)	NCI-10 (%lines)
8[6]	South 7, South 7	4.4	110	288	4.1	100	347	20	190	1.4	91	**96** (93)	**4.5** (100)
2[6]	North 1, South 7	25	138	271	11	27	480	37	31	7.9	23	**50** (87)	**16** (100)
11	*North G, South 7	>660	76	>650	9.3	56	>1000	45	>300	4.1	40	>105[a] (60)	≥**55** (90)
10	North G, South 7	1.2	76	>650	1.2	37	>1000	12	0.55	0.55	12	>34[a] (63)	**4.2** (100)
5[3]	North G*, South 7*	0.16	ip	ip	<0.1	ip	ip	ip	ip	<0.1	ip	ip	**1.0** (100)
4[4]	North G, North 1	1.6	7.4	65	0.99	3.4	140	9.7	3	0.10	1.8	**14** (96)	**3.8** (100)
15[4]	North G, South 1	>660	>760	>650	558	>120	>1000	>690	>300	617	>250	>900[a] (18)	>800[a] (60)
1[4]	North 1, South 1	0.20	0.40	6.3	<0.1	2.5	10	0.40	<0.1	<0.1	<0.1	**1.2** (100)	**0.8** (100)
7[8]	North 1, *South 1	0.12	0.59	1.1	<0.1	3.5	2.9	0.17	3.6	<0.1	0.22	**2.4** (97)	**0.8** (100)

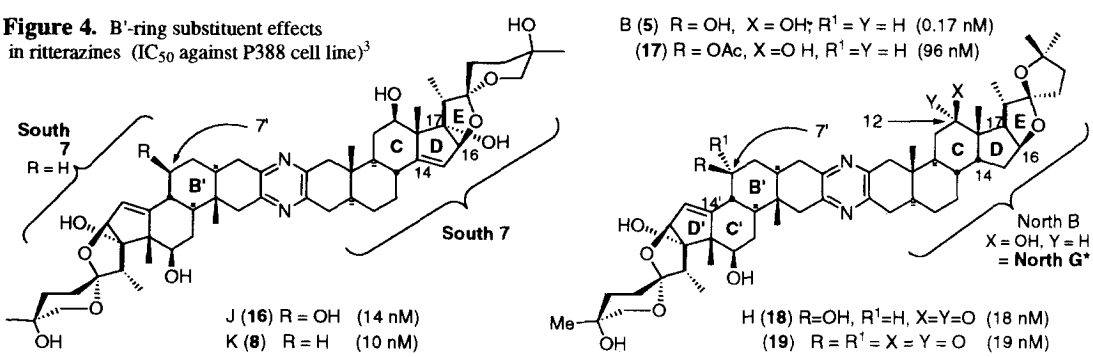
* modified "basic" subunits: *North G = 14*epi*-North B; North G* = North B; *South 1 = 14'α-South 1; South 7* = 7'OH-South 7.
(a) Lower limit only, no real average could be obtained due to insufficient % line response. (ip) in progress.

Natural **5** and **1**, derivatives **7** and **9**, and hybrid **4** show greater cytotoxicity than ritterostatin G_N7_S **10**, itself comparable or superior to cephalostatin 7 (**2**) and ritterazine K **8**. Ritterostatin G_N1_S (**15**, not shown) appears far less cytotoxic (only 11 of 60 lines affected).[4] This trend confirms the differential subunit requirement seen for the most active (1–10 nM) compounds of this class,[4,16b] reflecting the "polarity match" proposed earlier[3] and recently discussed in terms of membrane interaction.[17] For example, polar North 1 matches nonpolar North G (as in **4**) or South 1 (as in **1**) but is less differentiated from South 7 (in **2**), which is at least semipolar. North G partners well with North 1 or South 7 (as in **10**) but not nonpolar South 1 (as in **15**). Among the less active compounds (GI_{50}'s ~10^2 nM), it is interesting in this connection that ritterazine K **8**, the dimer of South 7 (which thus lacks any polarity difference in subunits), was found to be much less potent than cephalostatin 7 (**2**) vs P388 yet consistently showed activity comparable to **2** against human cells (Tables 2 and 3). The more polar North 1 dimer cephalostatin 12 (not shown), however, was weaker in both tests (P388 76 nM, GI_{50} 400 nM),[2] while the model North 1 dimer (not shown)[9d] derived from **12** was inactive (NCI: GI_{50} >2400 nM).

Synthesis of 7'-deoxyritterazine G (**10**) was intended to explore the role of the 7'OH group. Mechanics calculations of all pertinent compounds reveal the 7'H species to be superimposable with their 7'βOH relatives.[18] The upfield shift of H15' in the NMR relative to 7'H subunits[3] is consistent with the calculated topography (the 7'βOH points toward the $\Delta^{14'}$ moiety, but with no increase in the H-bonding term). A direct bioactivity comparison to scarce natural ritterazine G (**3**) is not yet possible, but **10** showed cytotoxicity often superior to **2** and **8** and generally only a factor of 10 lower than that of **5**, which was 5–fold more potent than **3** vs P388. This activity suggests, in contrast to previous conclusions,[3] that the 7'βOH present in many ritterazines has only a modest effect on potency. The SAR of ritterazines J (**16**) and K (**8**) is consistent with this view (Fig. 4). Moreover, 7'-acetylation of **5** to give **17** markedly diminished potency, but oxidation at 7' of ritterazine H (**18**) to give diketone **19** did not.[3] Specific electronic (inductive) or H-bond donor roles for the 7'OH thus seem unlikely. Rather, the contibution of the 7'OH to the overall identical oxidation states ("polarity") of the North 1 and 7'OH-South 7 units may be of greater significance in **3–6**.

The *trans* C/D ring-fused analogue of **5**, 14*epi*-7'deoxyritterazine B (**11**), was surprisingly less cytotoxic than 7'-deoxyritterazine G **10** in 2 day trials, a significant (100–fold) decrease from expectations. Ritterazine B **5** was more cytotoxic than ritterazines F (**6**) and G (**3**) vs P388.[3] Moreover, **5** showed activity comparable to **1** and consistently superior to **10** against human cells in all trials (Tables 2 and 3), and **1** was ~300–fold more potent than **10** in 2 day trials (Table 3). The 7'OH function was shown to be extraneous to high potency in **10**, and the *trans* C/D-fused analogue 14α-dihydrocephalostatin 1 (**7**, GI_{50} 2.4 nM) was nearly equipotent to its parent **1** (GI_{50} 1.2 nM).[8] We therefore anticipated that **11** would show high activity comparable to **5** and **1**, yet it affected even fewer cell lines than **10**, with GI_{50}'s generally 10^2 higher than those of **1** or **5** (Table 3).

Figure 4. B'-ring substituent effects in ritterazines (IC_{50} against P388 cell line)[3]



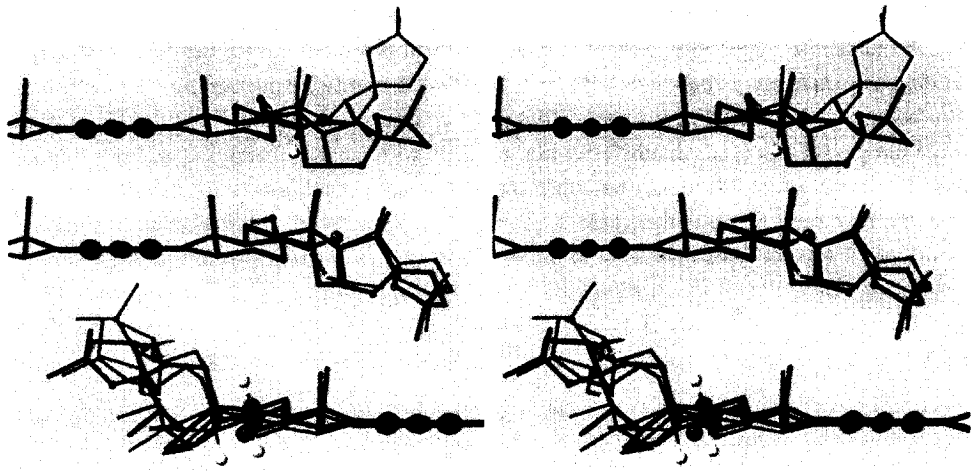


Figure 5. Stereoviews of natural (bold) and analogue (shadow) antineoplastics: (Top) North hemispheres of **5** vs **11**; (Middle) North hemispheres of **6** vs **10** (**3** is omitted since it overlaps perfectly with **10**); (Bottom) South hemispheres of **1** vs **7** and **9**.

The previously mentioned difference between **5** and **1** in the outer (D-F) rings may partially explain why **1** tolerates C/D alterations in one subunit but **5** does not. The D/E fusion (C13/C17) in the South 1 subunit type is unique (other types fuse at C16/C17). Calculations show a much greater topographical alteration in the outer (North D-F) rings for the 14α-analogue **11** vs its parent **5** than for those in the outer (South D-F) rings of 14α-analogue **7** vs its parent **1** (Figs. 5, 6 and Table 4).[18] For example, **7** shows a 3° change in the cant of its D/E [3.3.0] bicycle out of the pyrazine plane relative to that in **1**, whereas that of **11** changes 47° relative to **5**. The dihedral angle between spiroketal centers deviates 26° from **5** to **11**, but only 4° from **1** to **7**. Even smaller changes for analogue **9** vs its parent **1** include a slight shift in values toward those of **7** caused by H-bonding of the 12'βOH in **9** with the E-ring oxygen (Fig. 5), with a modest decrease in potency observed (Table 2).

Thus, in addition to its tolerance of D-ring saturation, the South 1 type unit is remarkably insensitive to the oxidation state at C12', in stark contrast to the 100-fold lower cytotoxicity of ritterazine H **18** (12-keto) relative to ritterazine B **5** (12βOH, Fig. 4) even though no difference in topography is calculated for **5** vs **18**. These results suggest that the C/D arrays fulfill more than a topographical purpose: *cis*-fused or 14-unsaturated non-South 1 (less flexible) steroids may also communicate enhanced ring strain and reactivity to distal functionality such as the spiroketal.[4] Preliminary calculations indicate this effect to be present in the **5/11** pair, but no strain difference was found between **1** and **7**.[18] Similarly, the sensitivity of North G and South 7 types to alteration at C12 may reflect distal reactivity changes as well as polarity effects. The presence of 14-unsaturation may be critical, as suggested by Winterfeldt,[16b,c] at least in one partner subunit.[8] None of the large collection of D,D'-

Figure 6. Overlay of cephalostatin 1 (**1**, bold) and ritterazine B (**5**, shadow). Nonpolar (South 1 and North B) units are oriented left, polar units to the right.

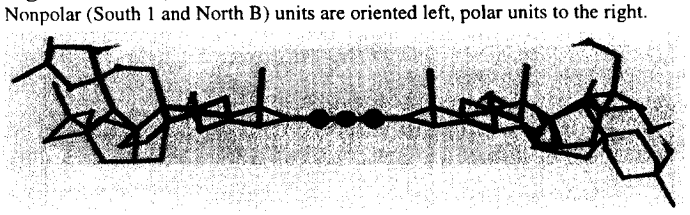


Table 4. Some calculated dimensions of selected bissteroidal pyrazines.

cpd	D/E cant	∠ pyr - C22	∠ pyr - C22'	∠ C22 - C22'	C22 - C22' Å
5	53.0°	-3.9°	-5.3°	-9.2°	22.6
11	5.6°	10.9°	-5.5°	16.4°	23.3
1	103°	1.5°	9.0°	10.5°	22.0
7	100°	0.9°	13.7°	14.8°	21.8

ring saturated compounds retain *in vitro* activity better than the micromolar range,[3,16] although no dual C/D *cis*-fused bissteroids with otherwise appropriately differentiated and polarity-matched subunits have been reported.

These SAR indications make no statement regarding clinical potential, but we believe their study will aid further planning and analogue preparations. We conclude that B-ring (7') oxidation *per se* is unnecessary for high *in vitro* potency but probably contributes to desirable polarity matching, and that the 12' oxidation state may vary in a unique subunit type (South 1) but not in others without significantly affecting cytotoxicity. A topographical role for the C/D fusion may be important, in that analogues which substantially alter the relative disposition of the D–F rings found in their parents show diminished activity. We speculate that the Δ^{14} or *cis*-fusion in non-South 1 subunit types may serve to enhance reactivity of functionality such as the spiroketal(s). A biochemical function in binding for homoallyl (and related 14-OH) C/D arrays,[19] in keeping with the proposed role of such an array in the biogenesis of 14-spiro subunits,[3] and in addition to that proposed for electrophilic oxacarbenium ions derived from spiroketal centers,[17,20] remains an intriguing possibility.

Acknowledgments: We thank the NIH (CA 60548), the Purdue Cancer Center (CG and TGL fellowships), and Proctor and Gamble (TGL fellowship) for financial support.

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