transformation to trichodiene.

The dienone **2** was prepared in 80% yield by the stannic chloride catalyzed acylation[9] of 1,4-dimethylcyclohexene[10] with the acid chloride of 2-methyl-1-cyclopentene carboxylic acid.[11] High yields were possible only when this reaction was performed by slow addition of 3 equiv of stannic chloride to a rapidly stirred solution of the acid chloride (generated in situ by treatment of the acid with oxalyl chloride) and 4 equiv of the cyclohexene in methylene chloride at −78 °C. The crude product was treated with sodium methoxide in methanol to dehydrohalogenate any β-chloro ketone material formed in the reaction. The cyclization of dienone **2** required more vigorous conditions than model compounds lacking the 2° methyl group on the cyclohexene ring.[8b,12] Thus, while cyclization of the model system proceeded readily in high yield upon treatment with trifluoroacetic acid,[8b] dienone **2** could not be cyclized to any significant extent with trifluoroacetic acid or mixtures of trifluoroacetic acid and trifluoroacetic anhydride. Reactions using Lewis acid catalysis[13] proved more fruitful. Reaction with 8 equiv of boron trifluoride etherate in refluxing chloroform for 5 days led to cyclization in 75–80% yield. The product was shown to be a diastereomeric mixture (ca. 2.4:1) of the cis-anti-cis and cis-anti-trans isomers of ketone **3**. Since the stereocenters other than at the quaternary carbons are immaterial to the synthesis, the mixture was used in further transformations.

Numerous reaction sequences were investigated[14] to find conditions to cleave the central five-membered ring, and the only useful reaction was found to be the Beckmann fragmentation reaction[15] of the oxime derived from ketone **3**. Reaction of ketone **3** with hydroxylamine gave oxime **4**, containing about 10% of the α,β-unsaturated isomer, in quantitative yield. Treatment of the oxime with trifluoroacetic anhydride followed by triethylamine gave the cyano dienes **5** and **6** (ratio varied from 3:1 to 6:1) in yields ranging from 45% to 60%. After an attempt to reduce both the diene system and the nitrile with lithium in ammonia failed,[16] the nitrile was reduced with lithium aluminum hydride to give the corresponding amino diene, which was reduced with lithium in ammonia to give amine **7a** in 80% yield. This amine was converted to the corresponding dimethyl derivative **7b** in 72% yield by reaction with formaldehyde and sodium cyanoborohydride followed by evaporative distillation.[17] Oxidation with *m*-chloroperoxybenzoic acid gave the amine oxide, which was heated at 150 °C under vacuum. The distillate was chromatographed on silica gel to give racemic trichodiene (**1**) in 40–44% overall yield from amine **7a**.[18] Examination of the product by ^{13}C and ^{1}H NMR spectroscopy showed no detectable signals attributable to the diastereomer, bazzanene.[19]

Thus, racemic trichodiene was synthesized in nine steps from 2-methyl-1-cyclopentenecarboxylic acid chloride. The possibility that this synthetic approach could also serve as a method for stereoselective synthesis of bazzanene through selective 1,2-reduction of diene **5** is currently under investigation.

Acknowledgment. We thank the Robert A. Welch Foundation (Grant A-442) for support of this research. The NMR spectrometers used in this research were purchased with the aid of National Science Foundation Grants to Texas A&M University.

Registry No. (±)-**1**, 61505-17-7; (±)-**2**, 91861-30-2; (±)-**3** (isomer 1), 91861-31-3; (±)-**3** (isomer 2), 91926-35-1; **4**, 91861-32-4; **5**, 91861-33-5; **6**, 91861-34-6; **7a**, 91861-35-7; **7b**, 91861-36-8; (±)-1,4-dimethylcyclohexene, 91926-34-0; 2-methyl-1-cyclopentenecarbonyl chloride, 59253-86-0.

Supplementary Material Available: Analytical and spectral data for structures **1–7b** (4 pages). Ordering information is given on any current masthead page.

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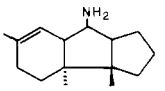

iv

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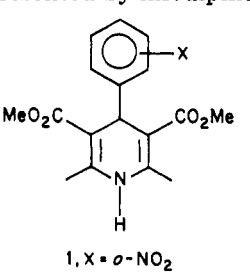
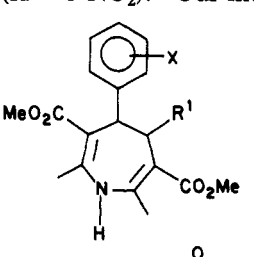
Synthesis of 4,5-Dihydroazepine-3,6-dicarboxylate Derivatives by Stereoselective Ring Expansion–Nucleophilic Addition to 4-(α-Chloroalkyl)-1,4-dihydropyridine-3,5-dicarboxylates

Summary: The synthesis of highly substituted 4,5-dihydroazepines by ring expansion of 1,4-dihydropyridines is described.

Sir: Among the various agents which block the transmembrane flux of calcium[1-3] are 1,4-dihydropyridine derivatives[4] originally prepared by Hantzsch[5] in 1882 and represented by nifedipine **1** (X = *o*-NO_2). Our interest



1, X = *o*-NO_2



2, R^1 = H, Me, Ph, $CH_2OC(=O)$-*t*-Bu

in the structural requirements of the dihydropyridine binding sites, proposed by Snyder[6] and others,[7] led us into

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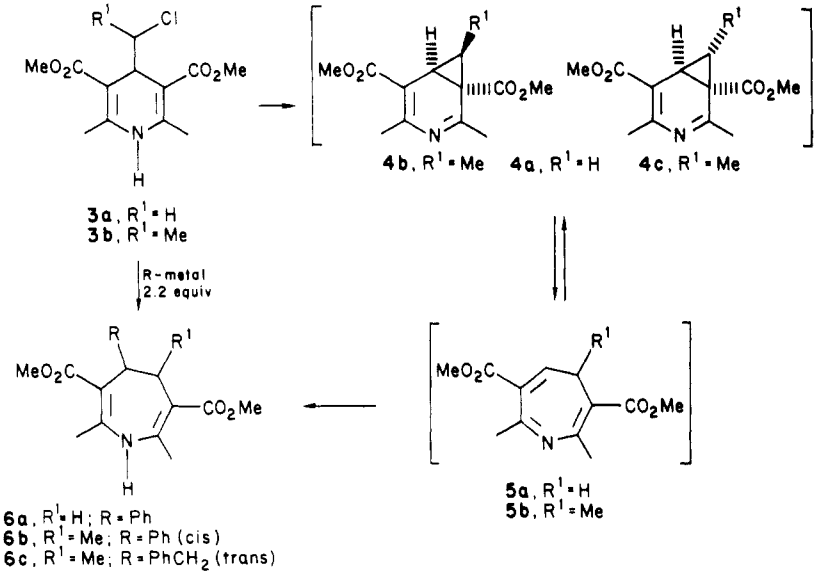
Scheme I



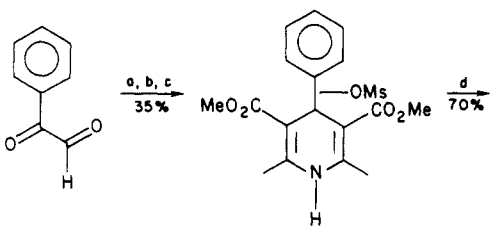
an exploration of this class of compounds.

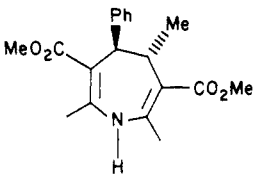
One of the questions we chose to investigate dealt with the effect of ring size, and this required a strategy for the synthesis of homologous Hantzsch products, i.e., 4-aryl-4,5-dihydroazepine-3,6-dicarboxylate derivatives **2**. Examples of this type have not been described previously, and we report here the first preparation of this class of compounds and the stereochemical results observed in the synthesis.

Based on precedent established by Johnson[8] and Gregory,[9] we envisaged (Scheme I) that a properly chosen organometallic reagent would react with dihydropyridine **3a**[8] by first generating the cyclopropane **4a** via intramolecular S_N2 reaction. Cyclopropane **4a** would be in equilibrium with azepine **5a** by a thermal disrotatory electrocyclic process.[10] Either **4a** or **5a** could react with a second equivalent of organometallic reagent effecting a conversion of **3a** to **6a**.

This approach to the synthesis of **2** was successful and the scope of the reaction as thus far demonstrated is summarized in Table I. Of the various organometallics studied, the Grignard reagents appear optimal as the source of base and nucleophile, combining high product yields (~80–90%) with ease of preparation. Sterically bulky Grignards (*tert*-butyl), aryl Grignards (ortho, meta, or para substituted), and aralkyl Grignards are suitable

Scheme II[a]





[a] (a) $CH_3C(NH_2)CHCO_2Me$, $CH_3C(O)CH_2CO_2Me$, THF, 65 °C; (b) $NaBH_4$, MeOH, 0 °C; (c) MsCl, Et_3N, DMF/CH_2Cl_2(1/3), −20 °C to 0 °C; (d) MeMgBr, THF, −78 to 0 °C.

reactants. Products[11] were isolated by either direct crystallization from the crude reaction mixture after extractive workup or after flash chromatography[12] on silica gel. They are stable at room temperature, in light, and on exposure to the atmosphere.

In order to study the stereochemistry of the reaction as reflected in the products, we investigated the conversion of **3b** (R^1 = Me) to **6b** (R^1 = Me). From inspection of models, it was not obvious whether the cis or trans isomers of **6b** would predominate. Addition of chlorodihydropyridine **3b** (R^1 = Me) in dry THF to 2.2 equiv of PhMgBr in THF at −78 °C and gradual warming to 0 °C over 3 h gave, after quenching with saturated aqueous NH_4Cl, a 12:1 mixture of two diastereomers of **6b** (R^1 = Me, R = Ph) in 90% combined yield. One recrystallization (toluene) separated the major isomer from the minor one. The ^1H NMR (360 MHz, $CDCl_3$) displayed $J_{4,5} < 1.0$ Hz for the

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(11) The structures for entries 1, 15, and 22 of Table I were confirmed by X-ray analysis. All entries exhibited spectroscopic data (360-MHz ^1H NMR, IR) consistent with proposed structures and correct combustion analysis (C, H, and N) within 0.4% of calculated.
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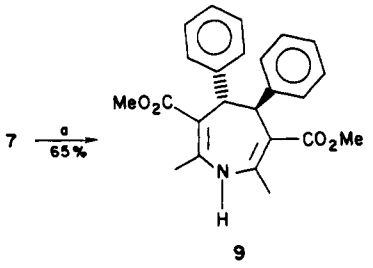
Table I. Reaction of 3a and 3b with Organometallic Reagents

entry	substrate	organometallic R-metal	reaction conditions[a] solvents, temp	products[b] yield,[c]	(cis/trans)	mp, °C
1	**3a**	PhMgBr	THF, Et_2O	92		135–7
2	**3a**	Ph_2CuLi	benzene, THF, Et_2O	90		135–7
3	**3a**	MeMgBr	THF, Et_2O	90		oil
4	**3a**	Me_2CuLi	THF, Et_2O	85		oil
5	**3a**	MeLi	THF, Et_2O	20		oil
6	**3a**	vinyl-MgBr	THF	95		82–4
7	**3a**	*t*-BuMgCl	THF	87		125–6
8	**3a**	cyclohexyl-MgCl	THF, Et_2O	73		112.5–3.5
9	**3a**	*n*-BuMgCl	THF, Et_2O	93		oil
10	**3a**	$(n\text{-Bu})_2Mg$	THF, heptane	78		oil
11	**3a**	*o*-CF_3PhMgBr	THF	80		157–8.5
12	**3a**	*m*-CF_3PhMgBr	THF	82		93–4
13	**3a**	*p*-CF_3PhMgBr	THF	87		105.5–6.5
14	**3a**	pentafluoro-PhMgBr	THF	85		117–8
15	**3b**	PhMgBr	THF	90	(12/1)[e]	122–2.5[d]
16	**3b**	PhMgBr	toluene	60	(3.5/1)[e]	122–2.5[d]
17	**3b**	PhMgBr	THF, 0 °C	75	(5/1)[e]	122–2.5[d]
18	**3b**	PhLi	benzene, THF, Et_2O	25	(5/1)[e]	122–2.5[d]
19	**3b**	*o*-CF_3PhMgBr	THF	75	(10/1)[f]	
20	**3b**	*p*-MeOPhMgBr	THF	83	(10/1)[f]	
21	**3b**	*p*-CF_3PhMgBr	THF	86	(10/1)[f]	
22	**3b**	$PhCH_2MgCl$	THF	85	(1/18)[f]	107–8[d]
23	**3b**	cyclohexyl-MgCl	THF, Et_2O	80	(<1/20)[g]	58–60
24	**3b**	vinyl-MgBr	THF	85	(<1/15)[f]	

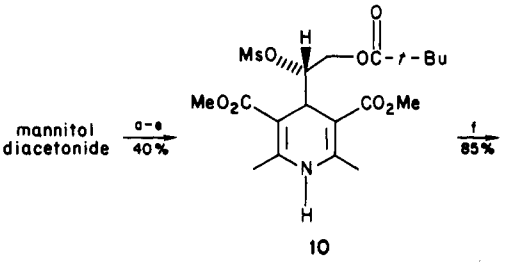
[a] Substrate dissolved in THF was treated with 2.2 equiv of organometallic at −78 °C and gradually warmed to 0 °C unless indicated otherwise. [b] Exhibited spectroscopic data consistent with the proposed structure. Stereoisomers assigned by ^1H NMR (see text). [c] For isolated homogeneous products exhibiting correct combustion analysis (C, H, N). [d] mp of major stereoisomer. [e] Determined by HPLC, ^1H NMR, and flash chromatographically separated wts. [f] Ratio obtained by ^1H NMR. [g] No cis isomer detected by ^1H NMR of crude product.

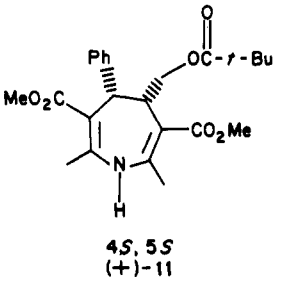
Scheme III[a]



[a] (a) PhMgBr, THF, −78 to 0 °C.

Scheme IV[a]





[a] (a) $Pb(OAc)_4$, THF, 0–25 °C; (b) $CH_3C(O)CH_2CO_2Me$, $CH_3C(NH_2)CHCO_2Me$, THF, 25 °C; (c) H_2O, Dowex 50 WX8, 85 °C, 30 min; (d) ClC(O)-*t*-Bu, pyr; (e) MsCl, Et_3N, CH_2Cl_2 −20 °C; (f) PhMgBr, THF, −78 to −10 °C.

major isomer and $J_{4,5}$ = 6.0 Hz for the minor. Single-crystal X-ray analysis[13] of the major product (Figure 1; supplementary material) confirmed the cis configuration.

As indicated in Table I (entries 15–24) a series of organometallic reagents was reacted with **3b** (R^1 = Me). Surprisingly, the nonaryl Grignard reagents produced major diastereomers of **6** (R^1 = Me) whose ^1H NMR (360 MHz, $CDCl_3$) displayed $J_{4,5} \geq 6.0$ Hz and minor isomers with $J_{4,5} \leq 2$ Hz (entries 22–24 of Table I). X-ray analysis[14] of the major isomer **6c** (R^1 = Me, R = $PhCH_2$) confirmed its identity as the trans isomer (Figure 2; supplementary material). Variations in solvent, temperature, and metal cation had modest effects on the stereoisomeric ratios but did not reverse the stereoselectivity. The products **6b** or **6c** did not epimerize under the reaction conditions.

In an attempt to determine whether cyclopropanes **4b** or **4c** were being formed preferentially in the presence of aryl or nonaryl Grignard reagents, the following experiments were conducted. An equivalent of PhMgBr was added to **3b** at −78 °C and after the mixture was slowly warmed to 0 °C and recooled to −78 °C, an equivalent of $PhCH_2MgCl$ was added, and the mixture was warmed to

(13) Crystals of **6b** formed from methanol with symmetry $P2_1/n$ and cell constants of a = 14.181 (1) Å, b = 7.483 (2) Å, c = 16.643 (1) Å, and β = 90.24 (1)°. Of the 2608 reflections measured by using an automatic four circle diffractometer, 2154 were observed and corrected for Lorentz and polarization effects. The structure was solved by using a multisolution tangent formula approach and refined by using full-matrix least squares. The function minimized was $\Sigma\omega(|F_o| - |F_c|)^2$ with $\omega = (1/\sigma F_o)^2$ to give an unweighted R factor of 0.050. Figure 1 is a drawing showing the relative stereochemistry and conformation of **6b**.

(14) Crystals of **6c** crystallized from methanol in space group $P\bar{1}$ with Z = 4 with cell dimensions of a = 12.175 (3) Å, b = 14.330 (2) Å, c = 11.779 (2) Å, α = 95.26 (1)°, β = 112.66 (2)°, and γ = 89.05 (2)°. A multisolution tangent formula approach with recycling of the original model solved the structure. Full-matrix least squares were used to minimize the 4358 observed ($I \geq 3\sigma I$) reflections in the function $\Sigma\omega(|F_o| - |F_c|)^2$ with $\omega = (1/\sigma F_o)^2$. The final unweighted residual was 0.047 after applying anisotropic temperature parameters for the non-hydrogen atoms and fixed isotropic temperature parameters for the hydrogen atoms. Figure 2 shows the conformation and configuration of one molecule of **6c** (the other differs in the conformation of side chains).

0 °C. A similar experiment was carried out in reverse sequence. Since no crossover contamination of **6b** (R = Ph) with **6c** (R = $PhCH_2$) occurred, and the isomer ratios were identical with those obtained under the usual conditions, we concluded that the same intermediates are generated with the various Grignard reagents. We have not been able to determine whether each intermediate, **4b**, **4c**, or **5b**, reacts with all organometallics or some combination react with certain organometallics preferentially.

Thus far, experiments with **3b** allow the following generalization. *Aryl Grignard reagents give cis products* with good stereoselectivity (≥10:1) and *nonaryl Grignard reagents give trans products* with excellent stereoselectivity (≥15:1).

The trans isomer **8** of cis **6b** was prepared in 70% yield by reacting mesylate **7** with 2.2 equiv of MeMgBr in THF as shown in Scheme II.

The only example of a trans stereospecific reaction with PhMgBr occurred when **7** was converted to 4,5-diphenyl-4,5-dihydroazepine **9** (determined by X-ray analysis) in 65% yield (Scheme III).

Reports of the enantioselectivity of the dihydropyridine receptor[15] prompted us to prepare optically active dihydroazepines. The strategy used employed D-mannitol diacetonide (Scheme IV) which was converted to the dihydropyridine mesylate **10**. Treatment of **10** with PhMgBr (2.2 equiv) in THF at −78 °C gave exclusively *cis*-dihydroazepine **11** ($J_{4,5}$ < 1 Hz) in 85% yield and 98% ee.[16] The absolute stereochemistry of **11** was assigned as shown ($[\alpha]^{25}_D$ +84.5° CH_3OH (*c* 3.30)).[17]

Using this ring expansion methodology we have prepared a variety of 4,5-substituted dihydroazepines in a stereo- and enantioselective manner. Furthermore, such dihydroazepines should provide tools for study of the dihydropyridine binding site.

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(16) Based on $Eu(hfbc)_3$ shifted ^1H NMR of the *tert*-butyl singlet which was cleanly separated in the racemic azepine prepared from *dl*-glyceraldehyde under similar conditions.
(17) Assuming an intramolecular S_N2 displacement of the mesylate to generate two diastereomeric cyclopropanes that would both give the same product **11** after further reaction.

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Registry No. **3a**, 3168-65-8; **3b**, 69891-46-9; **6a**, 91993-81-6; *cis*-**6b**, 91993-91-8; *trans*-**6b**, 91993-92-9; *cis*-**6c**, 91993-99-6; *trans*-**6c**, 91994-00-2; **6** (R^1 = H, R = Me), 91993-82-7; **6** (R^1 = H, R = CH_2=CH), 91993-83-8; **6** (R^1 = H, R = *t*-C_4H_9), 91993-84-9; **6** (R^1 = H, R = c-C_6H_{11}), 91993-85-0; **6** (R^1 = H, R = *n*-C_4H_9), 91993-86-1; **6** (R^1 = H, R = *o*-$CF_3C_6H_4$), 91993-87-2; **6** (R^1 = H, R = *m*-$CF_3C_6H_4$), 91993-88-3; **6** (R^1 = H, R = *p*-$CF_3C_6H_4$), 91993-89-4; **6** (R^1 = H, R = C_6F_5), 91993-90-7; *cis*-**6** (R^1 = Me, R = *o*-$CF_3C_6H_4$), 91993-93-0; *trans*-**6** (R^1 = Me, R = *o*-$CF_3C_6H_4$), 91993-94-1; *cis*-**6** (R^1 = Me, R = *p*-$MeOC_6H_4$), 91993-95-2; *trans*-**6** (R^1 = Me, R = *p*-$MeOC_6H_4$), 91993-96-3; *cis*-**6** (R^1 = Me, R = *p*-$CF_3C_6H_4$), 91993-97-4; *trans*-**6** (R^1 = Me, R = *p*-$CF_3C_6H_4$), 91993-98-5; *cis*-**6** (R^1 = Me, R = c-C_6H_{11}), 91994-01-3; *trans*-**6** (R^1 = Me, R = c-C_6H_{11}), 91994-02-4; *cis*-**6** (R^1 = Me, R = CH_2=CH), 91994-03-5; *trans*-**6** (R^1 = Me, R = CH_2=CH), 91994-04-6; **7**, 91994-08-0; **9**, 91994-05-7; **10**, 91994-06-8; **11**, 91994-07-9; $CH_3C(O)CH_2CO_2Me$, 105-45-3; $CH_3C(NH_2)CHCO_2Me$, 14205-39-1; $ClC(O)C(CH_3)_3$, 24608-52-4; PhCOCHO, 1074-12-0; PhMgBr, 100-58-3; Ph_2CuLi, 23402-69-9; MeMgBr, 75-16-1; Me_2CuLi, 15681-48-8; MeLi, 917-54-4; CH_2=CHMgBr, 1826-67-1; $(CH_3)_3CMgCl$, 677-22-5; c-$C_6H_{11}MgCl$, 931-51-1; $CH_3(CH_2)_3MgCl$, 693-04-9; $(CH_3(CH_2)_3)_2Mg$, 1191-47-5; *o*-$CF_3PhMgBr$, 395-47-1; *m*-$CF_3PhMgBr$, 402-26-6; *p*-$CF_3PhMgBr$, 402-51-7; C_6F_5MgBr, 879-05-0; PhLi, 591-51-5; *p*-MeOPhMgBr, 13139-86-1; $PhCH_2MgCl$, 6921-34-2; D-mannitol diacetonide, 1707-77-3.

Supplementary Material Available: Figures 1 and 2, and tables of the atomic positional and thermal parameters, bond distances and bond angles for **6b** and **6c**, selected NMR spectra and elemental analyses (14 pages). Ordering information is given on any current masthead page.

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Additions and Corrections

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Philip DeShong,* Subban Ramesh, and Joseph J. Perez. Total Synthesis of Tirandamycin. A Short, Efficient Synthesis of the Ireland Alcohol.

Page 2118. Reduction of ketone **10** with $Zn(BH_4)_2$ does not give alcohol **4** as the major product; instead alcohol **9**, the epimer of **4**, is the major alcohol formed. Scheme III should be modified accordingly.

Reduction of ketone **10** with $Zr(BH_4)_4$ gives a 1:1.7 mixture of alcohols **4** and **9**, respectively.

Edward C. Taylor,* David C. Palmer, Thomas J. George, Stephen R. Fletcher, Chi Ping Tseng, Peter J. Harrington, Donald J. Dumas, G. Peter Beardsley, Andre Rosowsky, and Michael Wick. Synthesis and Biological Activity of L-5-Deazafolic Acid and L-5-Deazaaminopterin: Synthetic Strategies to 5-Deazapteridines.

Page 4852. In the original paper the following should have been added to the listing of coauthors: Donald J. Dumas (Department of Chemistry, Princeton University), Andre Rosowsky and Michael Wick (Dana-Farber Cancer Institute).