temperature. After removal of the foil, the room lights being off, the ampule was broken open and the absorbance recorded. Absorbances were read to three decimal places with use of a Perkin-Elmer Lambda 3 spectrophotometer. The infinity readings were obtained by placing a foil-wrapped ampule of each set in a steam bath for at least 1 h before recording the absorbance.

B. For compounds obtained in small amounts, a variation on the above procedure was used. A solution with the appropriate concentration of the *trans*-azobenzene in isooctane was prepared, and about 3 mL was sealed in a 1-cm^2 quartz ampule. This ampule was irradiated in the RUL photoreactor in a water-cooled immersion well for at least 3 h. The constant-temperature bath described above was used to heat the cuvette holder of the spectrophotometer. The ampule was partially preheated in the reservoir of the constant-temperature bath before being placed into the heated cuvette holder. It was then left for 30–60 s to establish temperature equilibrium, and a zero time and absorbance were recorded. Between readings, a black-felt-covered card was placed in the light beams to prevent any photochemical isomerization. The infinity reading was obtained by placing the ampule in a steam bath in the dark for at least 1 h, putting it back in the spectrophotometer, waiting for temperature equilibration with the card in place, and finally recording the absorbance. The temperature was determined by using a similar unsealed ampule placed in the heated cuvette holder after the kinetic run was completed (usually while waiting for the infinity reading). This ampule was filled with isooctane to the same height as the sealed ampules. An electronic (thermistor) thermometer with a flexible cable was used to read the temperature.

Variable Temperature. C. Solutions and ampules were prepared as in method A and irradiated. The thermal isomerization was carried out by using a thermostated oil bath whose heater was controlled with a variable autotransformer. The temperature was measured with an electronic (thermistor) thermometer, the probe of which was placed in an ampule of isooctane similar to the test ampules. At suitable temperature intervals, one or more tubes were removed from the thermostat and cooled quickly in an ice bath. The corresponding temperature and time were recorded, and the absorbance was measured after the ampule was allowed to return to room temperature. The infinity readings were obtained by leaving one or more ampules in a steam bath for at least 1 h before recording their absorbances.

Data Analysis. Activation energies were calculated from the raw kinetic observations of absorbance, temperature, and time by a one-step procedure, full details of which will be published elsewhere. Briefly, the computational method consists of substituting the Arrhenius equation directly into the first-order rate expression (Abs, Abs_0, and Abs_{inf} are absorbances at time t, time 0, and the infinity reading).

Thus,

$$\int_0^t \frac{d(Abs - Abs_{inf})}{Abs - Abs_{inf}} = -\int_0^t k\, dt = -\int_0^t Ae^{-E_a/RT}\, dt \quad (1)$$

For a constant-temperature kinetic run, integration affords eq 2, while when the temperature varies, eq 1 must be integrated

$$Abs - Abs_{inf} = (Abs_0 - Abs_{inf}) \exp(-At \exp(-E_a/RT)) \quad (2)$$

numerically. In either case, an iterative procedure allows trial values of A and E_a to be fitted to the known values of Abs, Abs_0, time (t), and temperature (T).

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Supplementary Material Available: Final atomic coordinates, details of molecular geometry, and thermal parameters (9 pages). Order information is given on any current masthead page. A structure factor listing is available from G.F. (28 pages). Tables of all raw kinetic data are available from N.J.B. (18 pages).

Retinoids. 6.[1] Preparation of Alkyl- and Trimethylsilyl-Substituted Retinoids via Conjugate Addition of Cuprates to Acetylenic Esters[†]

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Five retinoids bearing the ethyl, *tert*-butyl, and trimethylsilyl groups in the 9-position of retinal and the ethyl and *tert*-butyl groups in the 13-position have been synthesized. The key step of the syntheses involves the conjugate addition of lithium diethylcuprate, lithium di-*tert*-butylcuprate, and lithium bis(trimethylsilyl)cuprate, respectively, to the acetylenic esters **4** and **13**. The stereoselectivity of this reaction was examined in detail; it proceeds stereoselectively cis in THF at −78 °C. Various isomers of the newly prepared retinoids were isolated by preparative HPLC and characterized by the usual spectroscopic methods. The dependence of the configuration and conformation of the polyene chain on the introduced group was studied by means of NMR and UV spectroscopy.

Introduction

Retinal (**1**) plays a pivotal role in two light energy converting processes, (i) the process of vision in vertebrates[2] and (ii) the proton pumping process in *Halobacterium halobium*;[3] the proteins responsible for these processes, rhodopsin and bacteriorhodopsin, respectively, both contain retinal as the prosthetic group[2,4] (Figure 1).

[†] Dedicated to Professor Dr. S. Hünig on the occasion of his 65th birthday.

[‡] Gesellschaft für Biotechnologische Forschung.

[§] Institut für Organische Chemie der Technischen Universität.

(1) Part 5: Hopf, H.; Krause, N. *Tetrahedron Lett.* **1985**, *26*, 3323–3326.

(2) Balogh-Nair, V.; Nakanishi, K. In Stereochemistry; Tamm, Ch., Ed.; Elsevier: Amsterdam, 1982; pp 283–334.

(3) (a) Oesterhelt, D. *Angew. Chem.* **1976**, *88*, 16–24; *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 17. (b) Henderson, R. *Annu. Rev. Biophys. Bioeng.* **1977**, *6*, 87–109.

(4) Oesterhelt, D.; Stoeckenius, W. *Nature (London), New. Biol.* **1971**, *233*, 149–152.

0022-3263/87/1952-0398$01.50/0

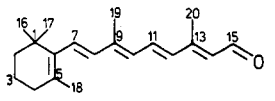

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Figure 1. *all-trans*-Retinal.[5]

One main strategy to analyze the interaction between the protein and the retinal molecule employs the introduction of retinal analogues (retinoids) into the protein;[2,6] the artificial chromoprotein thus formed shows an activity different from the original form, a fact that allows conclusions to be drawn about both the structure and mechanism of the protein.[2,3] Several hundreds of retinoids have been synthesized for this purpose by various research groups, whose work has been reviewed several times.[7] In order to simplify the interpretation, the modification of the retinoid should be either purely electronic or purely steric, an intention not readily met.

A steric modification of the retinal molecule may, for example, be introduced by the replacement of the methyl groups of the polyene chain by bulkier alkyl groups; however, as will be shown in this paper, an electronic modification is induced as well since the alkyl groups may cause configurational and conformational changes of the polyene chain. Several physical investigations on retinoids bearing the ethyl or the *n*-butyl group in the 9- and 13-position, respectively, have already been carried out, but no details on the syntheses of these retinoids were given.[8] Molecules bearing the ethyl or the propyl substituent in place of the 20-methyl group have been synthesized by Ermann and Bestmann,[9,10] who used Pommer's well-known vitamin A synthesis,[11] the key step being the Wittig condensation of the C_{15}-unit (β-ionylideneethyl)triphenylphosphonium bromide with the C_5 unit γ-acetoxytiglaldehyde. This method, however, suffers from several disadvantages that prevent its wider application: (i) it is necessary to synthesize a specific building block for each alkyl group to be introduced, (ii) it will be difficult to achieve a modification of the 9-position in 1 using these building blocks, and (iii) it proved impossible to introduce the particularly bulky and therefore interesting *tert*-butyl group by this method.[9] In view of these problems it appeared worthwhile to develop a different approach to alkyl-substituted retinoids, which should allow the deliberate introduction of different alkyl groups in either the 9- or 13-position by the use of a general synthetic scheme.

Scheme I. Synthesis of 19-Nor-9-ethylretinal (10a), 19-Nor-9-*tert*-butylretinal (10b), and 19-Nor-9-(trimethylsilyl)retinal (10c)

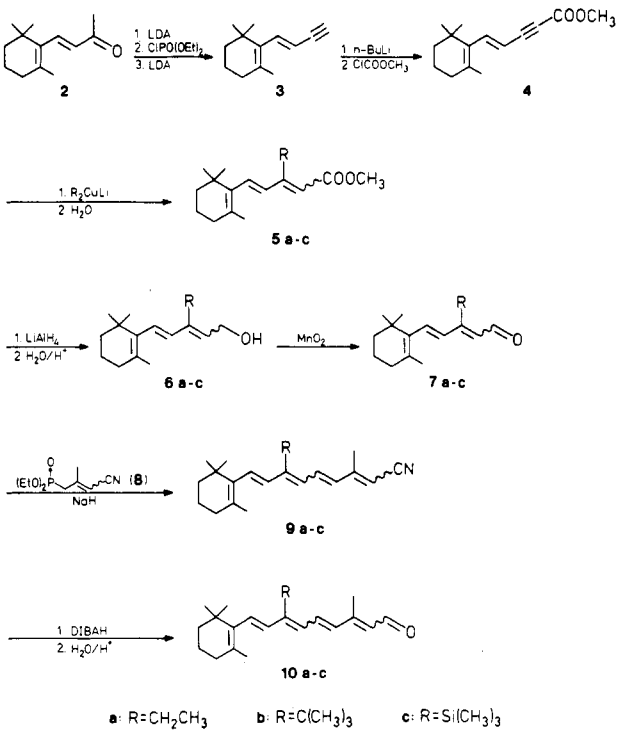


Table I. Solvent and Temperature Dependence of the Addition of Lithium Diethylcuprate to 4

solvent	temp, °C	time of reaction	quencher	*E*:*Z* ratio[a]
diethyl ether	0	5 min	methanol	49:51
diethyl ether	−78	1 h	methanol	13:87
diethyl ether	−78	1 h	water	32:68
THF	0	5 min	methanol	6:94
THF	−78	1 h	methanol	<1:99[b]

[a] Determined by ^{1}H NMR; the yield is higher than 80% in each experiment. [b] No (*E*)-**5a** detected.

In our previous work[1,12] we gained experience with acetylenic retinoids, and we therefore tried to develop a route to alkyl-substituted retinoids via an addition reaction to a triple bond. The conjugate addition of cuprates to acetylenic esters has been introduced by Corey[13] and has found application by several other authors.[14] Using this reaction for the first time in vitamin A chemistry, we synthesized four retinoids bearing an ethyl or a *tert*-butyl group in the 9- or the 13-position of retinal. This methodology could also be extended to the introduction of the trimethylsilyl group into the 9-position, and it should be applicable to other alkyl and silyl groups as well.

Results and Discussion

The synthesis of 19-nor-9-ethylretinal (**10a**), 19-nor-9-*tert*-butylretinal (**10b**), and 19-nor-9-(trimethylsilyl)retinal (**10c**) is summarized in Scheme I.

The acetylenic ester **4**, the key compound of this reaction sequence, was readily obtained in two steps from com-

(5) Nomenclature according to the IUPAC Comission on the Nomenclature of Organic Chemistry and the IUPAC–IUB Comission on Biochemical Nomenclature, *Carotenoids*; Isler, O., Ed.; Birkhäuser: Basel, 1971; pp 851–864. The numbering shown in structure 1 as well as the cis/trans nomenclature, which is convenient for carotenoids, is used throughout this paper. In *tert*-butyl- and trimethylsilyl-substituted retinoids, however, the cis/trans notation is not consistent with the *E*/*Z* nomenclature; e.g., 9-*cis*-**5b** = (9*E*)-**5b**; in such cases of doubt both designations are given.

(6) (a) Oesterhelt, D. *Methods Enzymol.* **1982**, *88*, 10–17. (b) Gärtner, W.; Oesterhelt, D.; Seifert-Schiller, E.; Towner, P.; Hopf, H.; Böhm, I. *J. Am. Chem. Soc.* **1984**, *106*, 5654–5659. (c) Gärtner, W.; Oesterhelt, D.; Towner, P.; Hopf, H.; Ernst, L. *J. Am. Chem. Soc.* **1981**, *103*, 7642–7643.

(7) (a) Balogh-Nair, V.; Nakanishi, K. *Methods Enzymol.* **1982**, *88*, 496–506. (b) Frickel, F. In *The Retinoids*; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Academic: Orlando, 1984; pp 7–145.

(8) (a) ^{13}C NMR data of 19-nor-9-ethylretinoic acid: Englert, G. *Helv. Chim. Acta* **1975**, *58*, 2367–2390. (b) Structure determination of 19-nor-9-ethylretinoic acid by X-ray diffraction: Schenk, H.; Kops, R. T.; van der Putten, N.; Bode, J. *Acta Crystallogr., Sect. B* **1978**, *34*, 505–507. (c) Resonance-Raman spectroscopy of 19-nor-9-*n*-butylretinal, 20-nor-13-*n*-butylretinal, and 19,20-dinor-9,13-di-*n*-butylretinal: Cookingham, R. E.; Lewis, A. *J. Mol. Biol.* **1978**, *119*, 569–577. (d) Resonance-Raman and IR spectroscopy of the retinoids mentioned under (c): Cookingham, R. E.; Lewis, A.; Lemly, A. T. *Biochemistry* **1978**, *17*, 4699–4711.

(9) (a) Ermann, P. Ph.D. Thesis, Erlangen-Nürnberg, 1982. (b) Bestmann, H. O.; Ermann, P.; Rueppel, H.; Sperling, W. *Liebigs Ann. Chem.* **1986**, 479–498.

(10) Schimz, A.; Sperling, W.; Ermann, P.; Bestmann, H. J.; Hildebrand, E. *Photochem. Photobiol.* **1983**, *38*, 417–423.

(11) Pommer, H. *Angew. Chem.* **1960**, *72*, 811–819.

(12) Krause, N.; Hopf, H.; Ernst, L. *Liebigs Ann. Chem.* **1986**, 1398–1406.

(13) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851–1852.

(14) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785–4786 and literature cited therein.

mercially available β-ionone (**2**). The preparation of the acetylenic hydrocarbon **3** has been reported by Negishi et al.[15] and proceeds via enolization of **2**, formation of the enol phosphate, and phosphate elimination; this reaction is particularly valuable since it represents the reversal of the well-known hydration of terminal acetylenes to methyl ketones. Metalation of **3** and reaction of the resulting lithium acetylide with methyl chloroformate according to a general procedure of Brandsma[16] furnished ester **4** in 71% yield. With this compound in hand the addition of lithium diethylcuprate was investigated in detail; the results obtained are as follows.

(i) Lithium diethylcuprate is usually prepared by addition of 2 equiv of ethyllithium[17] to 1 equiv of copper(I) iodide in diethyl ether or THF at 0 °C.[18,19] In order to achieve complete consumption of **4** it proved useful to employ up to 50% excess of lithium diethylcuprate with respect to **4**; this does not give rise to side reactions.

(ii) After addition of **4** in diethyl ether or THF solution to lithium diethylcuprate, the reaction is complete within 1 h at −78 °C or within 5 min at 0 °C. Subsequent quenching with methanol or water, extractive workup, and purification provides ester **5a** in more than 80% yield (cf. Experimental Section).

(iii) The sole reaction of the cuprate with **4** is the conjugate addition; no regioisomers are formed.

(iv) The stereoselectivity of the addition reaction may be controlled by means of the solvent and the reaction temperature as summarized in Table I.

In THF at −78 °C the addition proceeds stereoselectively cis; at higher temperatures, in diethyl ether or upon quenching with water instead of methanol this selectivity is lost, presumably because of increasing isomerization of the double bond in the enolate formed before quenching.[13] These results are in good agreement with those obtained by Corey et al.[13] for the addition of lithium dialkylcuprates to methyl 2-decynoate and methyl 2-butynoate. For the synthesis of 19-nor-9-ethylretinal (**10a**) this stereoselectivity was not required since we intended to prepare the 9-cis and 9-trans isomers of **10a** in one sequence and to separate them by preparative HPLC.

The subsequent steps leading to **10a** are standard procedures in vitamin A chemistry and were carried out without difficulties. Reduction of ester **5a** with $LiAlH_4$[20] (81%) and reoxidation with activated manganese dioxide[21] (53%) furnished aldehyde **7a**, which was converted to 19-nor-9-ethylretinonitrile (**9a**) by Wittig–Horner olefination with the anion of the C_5-phosphonate **8**[22] (89%). Reduction of **9a** with DIBAH[23] eventually provided the target molecule **10a** in 55% yield; the overall yield of **10a** from **4** is 17.7% (5 steps). The product mixture consisted of the four expected isomers 9-*cis*-, 9-*cis*,13-*cis*-, 13-*cis*, and *all-trans*-**10a**. The separation of the isomers by preparative HPLC proved to be difficult, and 9-*cis*, 13-*cis*- and 13-*cis*-**10a** could no be obtained in analytically pure form. Nevertheless it was possible to collect the ^1H and ^{13}C NMR data of all four isomers using 2D $^{13}C,^1H$ correlation spectroscopy (see paragraph at the end of the paper about supplementary material).

The synthesis of 19-nor-9-*tert*-butylretinal (**10b**) proceeded as described for **10a**; however, some differences should be emphasized. Lithium di-*tert*-butylcuprate is known to be thermally more labile than lithium diethylcuprate.[19] It is therefore prepared by addition of 2 equiv of commercially available *tert*-butyllithium solution in pentane to 1 equiv of copper(I) iodide in THF at −30 °C. After addition of **4**, stirring at −20 °C for 2 h is required to effect complete consumption of **4**; the conditions sufficient for the addition of lithium diethylcuprate (−78 °C, 1 h) provided only partial consumption of **4**. The resultant ester **5b**, obtained in 87% yield, consisted out of the 9-cis (9*E*) isomer exclusively, although the reaction conditions are rather vigorous compared with the preparation of **5a**. These findings are explained by the bulkiness of the *tert*-butyl group; in fact, it is remarkable that the *tert*-butyl group can be introduced into the 9-position of retinal since this position is sterically shielded by the methyl groups of the cyclohexene ring.

The subsequent steps proceeded without difficulty and afforded 19-nor-9-*tert*-butylretinal (**10b**) in 36.2% overall yield from **4** (5 steps). The product mixture consisted of 9-*cis*- and 9-*cis*,13-*cis*-**10b**, respectively; thus no isomerization of the 9,10 double bond has occurred on the way from **5b** to **10b**. This fact again illustrates the great steric demand of the 9-*tert*-butyl group.

A considerable extension of the methodology described for the introduction of alkyl groups could be achieved by the use of lithium bis(trimethylsilyl)cuprate for the conjugate addition to **4**. Silyl cuprates like $(PhMe_2Si)CuLi$[24] and $(Me_3Si)_2CuLi$[24,25] have been introduced into preparative organic chemistry by Fleming, who essentially examined the following reactions of these cuprates: (i) conjugate addition to α,β-unsaturated carbonyl compounds, in particular esters, (ii) conjugate displacement of tertiary allylic acetates, and (iii) addition to nonactivated terminal acetylenes.[24,25] Lithium bis(trimethylsilyl)cuprate, however, has found only little application since the trimethylsilyllithium required is not readily available; it is made either by treatment of bis(trimethylsilyl)mercury[26] with lithium[27] or by reaction of hexamethyldisilane with methyllithium.[28] We chose the latter method for the preparation of (trimethylsilyl)lithium, which by treatment with copper(I) iodide provided the desired cuprate.[25] The optimum conditions for the addition to **4** turned out to be a 15% excess of the cuprate, a temperature of −30 °C, and a reaction time of 2 h. Under these conditions the substrate was consumed completely; the product, however, contained not only the desired α,β-unsaturated ester **5c**, but also the product formed by a second addition of the cuprate to **5c**. This observation is not surprising since silyl cuprates are known to undergo conjugate addition reactions to α,β-unsaturated esters;[24,25] carbon cuprates show this reaction only in rare cases.[29]

(15) (a) Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A., Jr. *J. Org. Chem.* **1980**, *45*, 2526–2528. (b) Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.* **1985**, *64*, 44–49.

(16) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1971; pp 80–81.

(17) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981; pp 11–12.

(18) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615–5616.

(19) Posner, G. H. *Org. React.* **1975**, *22*, 253–400.

(20) Robeson, C. D.; Cawley, J. D.; Weisler, L.; Stern, M. H.; Eddinger, C. C.; Chechak, A. J. *J. Am. Chem. Soc.* **1955**, *77*, 4111–4119.

(21) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094–1111.

(22) Pommer, H.; Stilz, W. Ger. Patent 1 116 652; *Chem. Abstr.* **1962**, *57*, P2267d.

(23) Winterfeldt, E. *Synthesis* **1975**, 617–630.

(24) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520–2526.

(25) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805–1808.

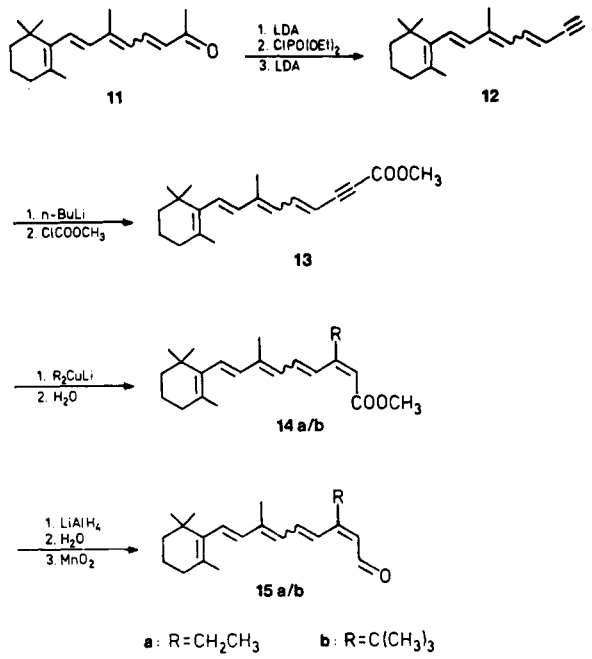
(26) Rösch, L.; Altnau, G.; Hahn, E.; Havemann, H. *Z. Naturforsch. B* **1981**, *36*, 1234–1237.

(27) Hengge, E.; Holtschmidt, N. *J. Organomet. Chem.* **1968**, *12*, P5–P7.

(28) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063–3064.

(29) Hallnemo, G.; Ullenius, C. *Tetrahedron Lett.* **1986**, *27*, 395–398 and literature cited therein.

Scheme II. Synthesis of 20-Nor-13-ethylretinal (15a) and 20-Nor-13-*tert*-butylretinal (15b)[a]



Since the ester **5c** could not be separated from its byproducts by column chromatography, it was subjected to the following steps without purification. The $LiAlH_4$ reduction to **6c** was carried out under the mild conditions described by Schwarzkopf et al.;[30] the aldehyde **7c** obtained after oxidation of the crude alcohol **6c** with activated manganese dioxide[21] could be purified by column chromatography without difficulties because the byproducts were no allylic alcohols and thus not oxidized. The aldehyde **7c** was isolated in 27% yield from **4**; as in the case of the *tert*-butyl analogue **7b**, it consisted of the 9-cis (9-*E*) isomer exclusively. The remaining steps to 19-nor-9-(trimethylsilyl)retinal (**10c**), the Wittig–Horner reaction with the anion of **8**[22] (55%) and the DIBAH reduction[23] of **9c** (55%) were carried out as usual and led to **10c** in a total yield of 8.2% (5 steps from **4**). The product composition resembles that of the *tert*-butyl retinoid **10b**; again solely the 9-cis and the 9-cis,13-cis isomer were formed.

Since the introduction of the alkyl and silyl groups into the 9-position of retinal proceeded so readily, it was obvious to apply this methodology to the 13-position as well. For this purpose the key intermediate, acetylenic ester **13**, had to be synthesized (see Scheme II).

Application of Negishi's method[15] to crude β-C_{18}-ketone **11**[31] actually provided the acetylenic hydrocarbon **12**, although in moderate yield (42%); this is presumably due to the formation of byproducts with allenic and retro structures as well as to the tendency of **12** to polymerize. The conversion of **12** to the acetylenic ester **13** according to Brandsma's procedure[16] proceeded without difficulty and lead to **13** in 55% yield.

The reaction of **13** with lithium diethylcuprate (50% excess) was carried out as described above; after stirring at −78 °C for 2 h the substrate had reacted completely. Ester **14a** obtained in 89% yield was reduced with $LiAlH_4$ to give the corresponding alcohol (procedure according to Schwarzkopf et al.[30]), which was treated with activated manganese dioxide[21] providing the target molecule 20-nor-13-ethylretinal (**15a**) in 49% yield. The product mixture consisted of 13-*cis*- and 9-*cis*,13-*cis*-**15a**; the addition of lithium diethylcuprate to **13** thus proceeded stereoselectively cis.

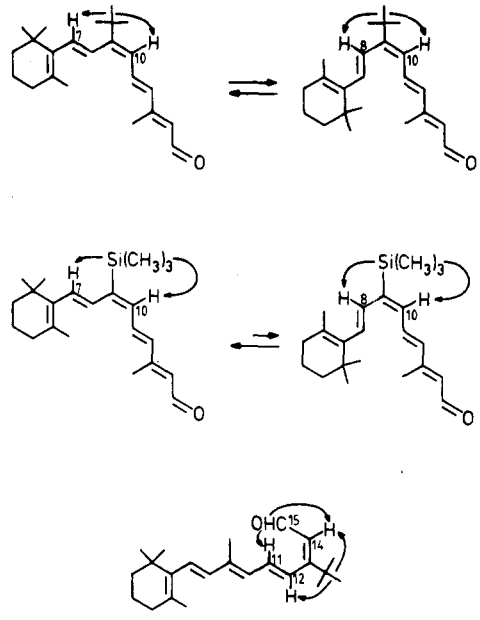


Figure 2. Nuclear Overhauser enhancements in 9-*cis*-**10b**, 9-*cis*-**10c**, and 13-*cis*-**15b**.

The scheme elaborated for the preparation of **15a** was applicable to the synthesis of 20-nor-13-*tert*-butylretinal (**15b**) without any changes. The addition of lithium di-*tert*-butylcuprate (30% excess) to acetylenic ester **13** was complete after 2 h at −78 °C. These conditions are rather mild relative to those necessary for the introduction of the *tert*-butyl group into the 9-position (−20 °C, 2 h). This fact again illustrates the better accessibility of the 13-position of retinal for bulky groups compared with the 9-position. Ester **14b** was obtained in 77% yield; reduction and reoxidation were performed as described for **14a** and provided 20-nor-13-*tert*-butylretinal (**15b**) in 59% yield. The product composition is identical with that of **15a**; i.e., 13-*cis*- and 9-*cis*,13-*cis*-**15b** were formed. Again, the addition of lithium di-*tert*-butylcuprate to **13** proceeded stereoselectively cis.

In view of the results presented so far it is surprising that the acetylenic ester **13** does not react with lithium bis(trimethylsilyl)cuprate; even after several hours at 0 °C the substrate remains unchanged. The reason for this behavior is not clear; experiments with less complex model compounds should be carried out and may provide an explanation.

After the description of the syntheses of the retinoids, it seems appropriate to shortly discuss their spectroscopic properties. The ^1H and ^{13}C NMR data of the isomeric retinals **10** and **15** are given as supplementary material (see paragraph at the end of the paper). The configurations of the ethyl analogues follow from a comparison of their ^1H and ^{13}C chemical shifts with those of the correspoding retinals **1**, which have recently been summarized and discussed by Liu et al.[32] This procedure is not applicable to the *tert*-butyl and trimethylsilyl analogues because these groups induce conformational changes which lead to atypical chemical shifts (see below). Therefore ^1H $\{^1H\}$ NOE difference spectra[33] were recorded. When the *tert*-

(30) Schwarzkopf, O.; Cahnmann, H. J.; Lewis, A. D.; Swidinsky, J.; Wüest, H. M. *Helv. Chim. Acta* **1949**, *32*, 443–452.
(31) Huisman, H. O.; Smit, A.; van Leeuwen, P. H.; van Rij, J. H. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 977–1006.
(32) Liu, R. S. H.; Asato, A. E. *Tetrahedron* **1984**, *40*, 1931–1969.
(33) Sanders, J. K. M., Mersh, J. D. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *15*, 353–400, in particular pp 361–380.

Table II. UV Data of Retinal[32] and the Retinoids Prepared in This Work

	λ_{max}, nm (ϵ)			
	all-trans	9-cis	13-cis	9-cis,13-cis
1[a]	383 (42 884)	373 (36 010)	375 (35 500)	368 (32 380)
10a[b]	387 (38 200)	380 (33 900)		
10b[b]		354 (25 900)		350 (24 500)
10c[b]		373 (21 700)		365 (18 400)
15a[b]			382 (27 600)	382 (23 100)
15b[b]			[c]	[c]

[a] In ethanol. [b] In dichloromethane. [c] The UV spectra exhibit no distinct absorption maxima: 13-*cis*-**15b**: λ_{max} (ϵ) 230 (13 700), 253 (13 100), 337 (16 300), 364 nm (15 500). 9-*cis*,13-*cis*-**15b**: λ_{max} (ϵ) 232 (14 000, shoulder), 252 (15 900), 290 (13 800), 322 (13 000), 333 (12 200, shoulder), 357 nm (9800, shoulder).

butyl resonance in 9-*cis*-**10b** was saturated, enhancements were observed of the 7-H, 8-H, and 10-H signals. This proves the 9-cis configuration and shows that more than one conformer with respect to the C(8)–C(9) single bond is involved (see Figure 2). Chemical shift comparison then led to the configuration of the C(9)–C(10) double bond in 9-*cis*,13-*cis*-**10b**.

A similar result was obtained for the trimethylsilyl derivative **10c**. Saturation of the trimethylsilyl signal in 9-*cis*-**10c** caused strong enhancements of the 7-H and 10-H resonances and a weak enhancement of the 8-H resonance; this result proves the 9-cis configuration and reveals the presence of both 8-s-cis and 8-s-trans conformers, the latter being more highly populated than in the *tert*-butyl analogue (see Figure 2). By chemical shift comparison the second isomer of **10c** was shown to have the 9-cis,13-cis configuration. In a similar way, the configurations of the C(13)–C(14) double bonds in both isomers of **15b** were shown to be cis. Saturation of the 13-*tert*-butyl resonance in 13-cis-**15b** gave enhancements of the 12-H and 14-H signals; saturation of the aldehyde proton resonance enhanced the 11-H and 14-H signals. Besides proving the 13-cis configuration, these experiments indicate a preference for the 12-s-cis (or a closely related gauche) conformation (see Figure 2).

Conformational control of polyenes by the *tert*-butyl and similar bulky groups is not a new finding; a particularly well-known example is 2-*tert*-butyl-1,3-butadiene. The first hint for the preference of a s-cis conformation in this molecule was its high reactivity in Diels–Alder reactions[34] and in the addition of SO_2;[35] direct proof for the presence of this conformation was received from several spectroscopic investigations.[36-38]

An impression of the influence of the newly introduced group on the polyene chain can also be obtained by comparison of the ^1H and ^{13}C NMR chemical shifts of the retinoids with those of retinal.[32] As expected, the values for the ethyl analogues are similar to those of retinal except in the immediate vicinity of the ethyl substituent, whereas the *tert*-butyl and the trimethylsilyl group influence greater parts of the molecule.

Similar conclucions can be drawn from the comparison of the UV data of the newly prepared retinoids with those of retinal (see Table II).

Again, the retinoids bearing the ethyl substituent in the 9- or 13-position, respectively, behave similarly to retinal; in contrast the 9-*tert*-butyl derivative **10b** exhibits a hypsochromic shift of 20–30 nm with a concomitant decrease of the extinction coefficient. It is obvious that the bulky *tert*-butyl group diminishes the degree of conjugation in the retinal molecule, probably by repulsive interactions with the adjacent hydrogen atoms of the polyene chain and subsequent distortion of the molecule. In the case of the 9-trimethylsilyl analogue **10c** this effect is weaker, presumably due to the electropositivity of the Me_3Si group and its greater distance from the polyene chain. Finally, the isomers of 20-nor-13-*tert*-butylretinal (**15b**) show a completely different behavior; the spectra have no similarity with those of retinal. Instead of the strong long-wave band (α-band) of retinal, they possess several bands at shorter wavelengths (β-bands), a behavior that is known from several isomers of retinal with a preference of a twisted 12-s-cis conformation.[39] Hence, this observation confirms the result of the NOE experiments.

Conclusion

The addition of cuprates to the readily accessible acetylenic esters **4** and **13** represents a novel, flexible way to retinoids bearing alkyl and silyl groups in the 9- and 13-position, respectively; in the present work five retinoids have been synthesized by this method. The reaction proceeds even with bulky groups like the *tert*-butyl and the trimethylsilyl groups; the only exception is the introduction of the Me_3Si group into the 13-position of retinal, which could not be achieved. In principle, this approach should be applicable to all alkyl and silyl groups, provided that the corresponding lithium compound can be prepared and that the group is not too bulky to be inserted into the molecule.

The newly synthesized retinoids possess several interesting features, the most intriguing one being the influence of the introduced group on the configuration and conformation of the polyene chain. In the ethyl analogues the adjacent doubld bond of the polyene chain can exist in the cis or trans configuration; the conformation resembles that of retinal. In the *tert*-butyl and trimethylsilyl retinoids, on the other hand, the adjacent double bond is forced into the cis configuration; furthermore the s-cis conformation of the neighboring single bond is increasingly favored in the series 9-Me_3Si < 9-*tert*-butyl < 13-*tert*-butyl. Thus the introduction of voluminous groups represents a way to control the configuration and conformation of the polyene chain and to make retinoids to measure.

Experimental Section

Materials. Diethyl ester and THF were distilled from $LiAlH_4$. β-Ionone was distilled under vacuum. All other reagents were of analytical grade and were used without further purification.

Analyses. ^1H NMR spectra were recorded on a Varian T-60 (CCl_4), a Bruker AM 300 ($CDCl_3$), or a Bruker WM 400 spectrometer ($CDCl_3$) with $(CH_3)_4Si$ as the internal standard. ^{13}C NMR spectra were obtained on a Bruker AM 300 or a Bruker WM 400 spectrometer with $CDCl_3$ as the solvent and the internal standard (δ 77.05). The ^{13}C NMR spectra of 9-cis-**10b** and of all isomers of **10a**, **10c**, **15a**, and **15b** were assigned by two-dimen-

(34) (a) Craig, D.; Shipman, J. J.; Fowler, R. B. *J. Am. Chem. Soc.* **1961**, *83*, 2885–2891. (b) Bartlett, P. D.; Wallbillich, G. E. H.; Wingrove, A. S.; Swenton, J. S.; Montgomery, L. K.; Kramer, B. D. *J. Am. Chem. Soc.* **1968**, *90*, 2049–2056.

(35) Isaacs, N. S.; Laila, A. A. R. *Tetrahedron Lett.* **1976**, 715–716; *J. Chem. Res. Synop.* **1977**, 10–11.

(36) ^1H NMR spectroscopy: (a) Hobgood, Jr., R. T.; Goldstein, J. H. *J. Mol. Spectrosc.* **1964**, *12*, 76–86. (b) Bothner-By, A. A.; Harris, R. K. *J. Am. Chem. Soc.* **1965**, *87*, 3451–3455.

(37) ^{13}C NMR spectroscopy: (a) Hasegawa, K.; Asami, R.; Takahashi, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 916–920. (b) Erusalimskii, G. B.; Druz, N. N.; Lobach, M. I.; Kormer, V. A. *Zh. Org. Khim.* **1978**, *14*, 2021–2024.

(38) UV spectroscopy: Moskvin, A. F.; Kusakov, M. M.; Doktorova, L. I.; Emel'yanova, A. A. *Zh. Prikl. Spektrosk.* **1973**, *19*, 157.

(39) Knudsen, C. G.; Chandraratna, R. A. S.; Walkeapää, L. P.; Chauhan, Y. S.; Carey, S. C.; Cooper, T. M.; Birge, R. R.; Okamura, W. H. *J. Am. Chem. Soc.* **1983**, *105*, 1626–1631.

sional $^{13}C/^{1}H$ chemical shift correlation experiments. These used the pulse sequence described by Rutar[40] which eliminates vicinal couplings in the ^{1}H dimension and thus gives improved sensitivity. $^{1}H\{^{1}H\}$ NOE difference spectra[33] were recorded at 300 MHz by accumulating separate free induction decays for the on-resonance irradiations and the control spectrum: prescan saturation time 10 s, decoupler power level 50 dB below 0.2 W. IR spectra were recorded on a Perkin-Elmer 1420, UV spectra on a Beckman UV 5230 spectrometer. Mass spectra (electron impact ionization, 70 eV) were obtained on a Varian MAT CH-7 or a MAT 8222 spectrometer, exact masses were determined on the latter instrument or a Varian MAT 731. Column chromatography was carried out with silica gel 70–230 mesh (Merck) or aluminum oxide activity II–III (Woelm) and cyclohexane/diethyl ether 80/20 (v/v) as the eluent. HPLC analyses were accomplished with a DuPont Model 830 chromatograph and a DuPont UV spectrophotometer (wavelength used: 330 nm). A 4.6 × 250 mm column was used for analytical and a 25 × 500 mm column for preparative HPLC, both charged with 7-μm SI 60 silica gel. Eluents employed were cyclohexane/diethyl ether 80/20 (v/v) for **10**, 90/10 (v/v) for **15a**, and 95/5 (v/v) for **15b**, respectively.

Methyl 5-(2,6,6-Trimethylcyclohexen-1-yl)-4-penten-2-ynoate (4). A solution of 4.36 g (25 mmol) of **3**[15] in 20 mL of diethyl ether was cooled to −78 °C, and 13.2 mL of *n*-butyllithium (25 mmol, 1.9 M solution in hexane) was added. The mixture was warmed to −50 °C, and 3.31 g (35 mmol) of methyl chloroformate was added in one portion. The mixture was stirred at −30 °C for 2 h and allowed to reach room temperature within 4 h. Hydrolysis on ice was followed by extraction with diethyl ether and drying. The crude product obtained after evaporation of the solvent was purified by kugelrohr distillation (110 °C/0.01 mbar), yielding 4.11 g of ester **4** (17.7 mmol, 71%) as an orange oil: IR (CCl_4) ν 2200, 1705 cm^{-1}; ^{1}H NMR (300 MHz) δ 6.96 (d, 1 H, 7-H, $J_{7,8}$ = 16.5 Hz), 5.57 (d, 1 H, 8-H), 3.80 (s, 3 H, 11-OCH_3), 2.04 (m, 2 H, 4-H), 1.74 (s, 3 H, 5-CH_3), 1.64–1.56 (m, 2 H, 3-H), 1.47–1.43 (m, 2 H, 2-H), 1.03 (s, 6 H, 1-CH_3); ^{13}C NMR δ 154.3 (s, 11-C), 147.6 (d, 7-C), 136.6 and 134.5 (both s, 5-C and 6-C), 108.4 (d, 8-C), 86.8 and 80.6 (both s, 9-C and 10-C), 52.3 (q, 11-OCH_3), 39.6 (t, 2-C), 33.9 (s, 1-C), 33.3 (t, 4-C), 28.6 (q, 1-CH_3), 21.4 (q, 5-CH_3), 18.9 (t, 3-C); UV (ethanol) λ_{max} (ϵ) 301 nm (12700); MS, *m/e* 232 (M^+); exact mass calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1463 ± 0.0005.

Methyl 3-Ethyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadienoate (5a). A suspension of 3.81 g (20 mmol) of copper(I) iodide in 15 mL of diethyl ether was cooled to 0 °C, and 32 mL of ethyllithium (40 mmol, 1.25 M solution in diethyl ether[17]) was added dropwise. The resultant black solution was cooled to −78 °C and treated with 3.00 g (12.9 mmol) of **4** in 10 mL of diethyl ether. The mixture was stirred at −78 °C for 1 h, hydrolyzed with 1 mL of water, and allowed to reach room temperature. Extractive workup, drying, and evaporation of the solvent provided crude ester **5a**, which was purified by kugelrohr distillation (120 °C/0.01 mbar); yield, 2.85 g of **5a** (10.9 mmol, 84%), colorless liquid. The 9-*E*/*Z* ratio (determined by ^{1}H NMR) was 32:68. IR (CCl_4): ν 1720 cm^{-1}. ^{1}H NMR (300 MHz) (9*E*)-**5a**: δ 6.58 (d, 1 H, 7-H, $J_{7,8}$ = 16.2 Hz), 5.97 (d, 1 H, 8-H), 5.68 (s, 1 H, 10-H), 3.71 (s, 3 H, 11-OCH_3), 2.87 (q, 2 H, 9-CH_2, J = 7.5 Hz), 2.02 (m, 2 H, 4-H), 1.70 (s, 3 H, 5-CH_3), 1.66–1.56 (m, 2 H, 3-H), 1.49–1.43 (m, 2 H, 2-H), 1.15 (t, 3 H, 9-CCH_3), 1.02 (s, 6 H, 1-CH_3). ^{1}H NMR (9*Z*)-**5a**: δ 7.53 (d, 1 H, 8-H, $J_{7,8}$ = 16.6 Hz), 6.61 (d, 1 H, 7-H), 5.65 (s, 1 H, 10-H), 3.70 (s, 3 H, 11-OCH_3), 2.44 (q, 2 H, 9-CH_2, J = 7.5 Hz), 2.04 (m, 2 H, 4-H), 1.77 (s, 3 H, 5-CH_3), 1.66–1.56 (m, 2 H, 3-H), 1.49–1.43 (m, 2 H, 2-H), 1.17 (t, 3 H, 9-CCH_3), 1.06 (s, 6 H, 1-CH_3). ^{13}C NMR (9*E*)-**5a**: δ 167.1 (s, 11-C), 159.4 (s, 9-C), 137.3 (s, 6-C), 134.6 and 133.5 (both d, 7-C and 8-C), 130.8 (s, 5-C), 116.4 (d, 10-C), 50.8 (q, 11-OCH_3), 39.6 (t, 2-C), 34.3 (s, 1-C), 33.0 (t, 4-C), 28.9 (q, 1-CH_3), 21.6 (q, 5-CH_3), 20.9 (t, 9-CH_2), 19.2 (t, C-3), 14.2 (q, 9-CCH_3). ^{13}C NMR (9*Z*)-**5a**: δ 167.1 (s, 11-C), 157.4 (s, 9-C), 137.4 (s, 6-C), 133.9 (d, 7-C), 131.7 (s, 5-C), 129.0 (d, 8-C), 114.2 (d, 10-C), 50.8 (q, 11-OCH_3), 39.9 (t, 2-C), 34.2 (s, 1-C), 33.3 (t, 4-C), 29.0 (q, 1-CH_3), 27.0 (t, 9-CH_2), 21.7 (q, 5-CH_3), 19.2 (t, 3-C), 13.8 (q, 9-CCH_3). MS, *m/e* 262 (M^+); exact mass calcd for $C_{17}H_{26}O_2$ 262.1933, found 262.1933 ± 0.0005.

(40) Rutar, V. *J. Magn. Reson.* **1984**, *58*, 306–310.

3-Ethyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadien-1-ol (6a). To a suspension of 0.38 g (10 mmo) of $LiAlH_4$ in 10 mL of diethyl ether was added 2.49 g (9.5 mmol) of **5a** in 15 mL of diethyl ether at 0 °C. The mixture was stirred at room temperature for 1 h and hydrolyzed, and the precipitate formed was dissolved in 1 N hydrochloric acid. Extractive workup, drying, evaporation of the solvent, and kugelrohr distillation (120 °C/0.01 mbar) furnished 1.80 g of **6a** (7.7 mmol, 81%) as a colorless liquid: IR (CCl_4) ν 3620, 3600–3200 cm^{-1}; ^{1}H NMR (60 MHz) δ 6.2–5.9 (m, 2 H, 7-H, 8-H), 5.50 (t, 1 H, 10-H, $J_{10,11}$ = 6 Hz), 4.20 (d, 1 H, 11-H), ~2.3 (q, 2 H, 9-CH_2, J = 7 Hz), 2.2–2.0 (m, 2 H, 4-H), 1.70 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), ~1.2 (t, 3 H, 9-CCH_3), 1.02 (s, 6 H, 1-CH_3); MS, *m/e* 234 (M^+); exact mass calcd for $C_{16}H_{26}O$ 234.1984, found 234.1984 ± 0.0005.

3-Ethyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadienal (7a). To 1.59 g (6.8 mmol) of **6a** in 150 mL of diethyl ether was added 21.7 g (0.25 mol) of activated manganese dioxide, and the mixture was stirred at room temperature for 17 h. The manganese dioxide was filtered off, and the solvent was evaporated. The crude aldehyde was purified by column chromatography yielding 0.84 g of **7a** (3.6 mmol, 53%) as a yellow oil: 9-*E*/*Z* ratio (determined by ^{1}H NMR), ~1:2; IR (CCl_4) ν 1675 cm^{-1}. ^{1}H NMR (60 MHz) (9*E*)-**5a**: δ 10.15 (d, 1 H, 11-H, $J_{10,11}$ = 8 Hz), 6.48 (d, 1 H, 7-H, $J_{7,8}$ = 16 Hz), 6.02 (d, 1 H, 8-H), 5.80 (d, 1 H, 10-H), 2.83 (q, 2 H, 9-CH_2, J = 7 Hz), 2.2–2.0 (m, 2 H, 4-H), 1.77 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.22 (t, 3 H, 9-CCH_3), 1.07 (s, 6 H, 1-CH_3). ^{1}H NMR (9*Z*)-**5a**: δ 10.15 (d, 1 H, 11-H, $J_{10,11}$ = 8 Hz), 6.95 (d, 1 H, 8-H, $J_{7,8}$ = 16 Hz), 6.48 (d, 1 H, 7-H), 5.80 (d, 1 H, 10-H), 2.47 (q, 2 H, 9-CH_2, J = 7 Hz), 2.2–2.0 (m, 2 H, 4-H), 1.77 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.22 (t, 3 H, 9-CCH_3), 1.07 (s, 6 H, 1-CH_3); MS, *m/e* 232 (M^+); exact mass calcd for $C_{16}H_{24}O$ 232.1827, found 232.1827 ± 0.0005.

19-Nor-9-ethylretinonitrile (9a). A suspension of 0.2 g of sodium hydride (5 mmol, 60% in mineral oil) in 5 mL of THF was treated with 1.09 g (5 mmol) of phosphonate **8**[22] in 5 mL of THF within 30 min. The mixture was stirred for 1 h and 0.74 g (3.2 mmol) of **7a** in 2 mL of diethyl ether was added in one portion at 0 °C. The mixture was stirred at room temperature for 3 h and hydrolyzed. Extractive workup, drying, evaporation of the solvent, and column chromatography provided 0.84 g of **9a** (2.8 mmol, 89%) as a yellow oil: IR (CCl_4) ν 2210 cm^{-1}; ^{1}H NMR (60 MHz) δ 7.2–5.8 (m, 5 H, 7-H, 8-H, 10-H, 11-H, 12-H), 5.2–5.0 (m, 1 H, 14-H), 2.38 (q, 2 H, 9-CH_2, J = 7 Hz), 2.22 (s, 3 H, 13-CH_3), 2.2–2.0 (m, 2 H, 4-H), 1.73 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.15 (t, 3 H, 9-CCH_3), 1.05 (s, 6 H, 1-CH_3); MS, *m/e* 295 (M^+); exact mass calcd for $C_{21}H_{29}N$ 295.2300, found 295.2300 ± 0.0006.

19-Nor-9-ethylretinal (10a). To 443 mg (1.5 mmol) of **9a** in 8 mL of hexane was added 4.0 mL of DIBAH (4.0 mmol, 1.0 M solution in hexane) at 0 °C. The mixture was stirred for 3 h at room temperature, 1 mL of methanol was added at 0 °C, and after the mixture had been stirred at room temperature for 15 min, the precipitate formed was dissolved in 1 N hydrochloric acid. Extractive workup was followed by drying, evaporation of the solvent, and column chromatography, yielding 245 mg of **10a** (0.82 mmol, 55%), a yellow oil. The mixture of isomers was analyzed by HPLC and consisted of 20% 9-*cis*,13-*cis*-, 8% 13-*cis*-, 52% 9-*cis*-, and 20% *all-trans*-**10a**, respectively. It proved impossible to separate 9-*cis*,13-*cis*- and 13-*cis*-**10a** from each other completely by preparative HPLC. IR (CCl_4, *all-trans*-**10a**): ν 1670 cm^{-1}. ^{1}H and ^{13}C NMR: see paragraph at the end of the paper about supplementary material. UV: see Table II. MS: *m/e* 298 (M^+); exact mass calcd for $C_{21}H_{30}O$ 298.2297, found 298.2297 ± 0.0006.

Methyl 3-*tert*-Butyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadienoate (5b). A suspension of 3.62 g (19 mmol) of copper(I) iodide in 15 mL of THF was treated with 24.2 mL of *tert*-butyllithium (38 mmol, 15% solution in pentane) at −30 °C; 2.84 g (12.2 mmol) of **4** in 15 mL of THF was added at −30 °C, and the mixture was stirred at −20 °C for 2 h. After addition of 2 mL of methanol, workup was carried out as usual. Kugelrohr distillation of the crude ester (110 °C/0.002 mbar) yielded 3.10 g of **5b** (10.7 mmol, 87%) as a pale yellow liquid: IR (CCl_4) ν 1730 cm^{-1}; ^{1}H NMR (300 MHz) δ 6.17 (d, 1 H, 8-H, $J_{7,8}$ = 16.2 Hz), 6.08 (d, 1 H, 7-H), 5.68 (s, 1 H, 10-H), 3.62 (s, 3 H, 11-OCH_3), 1.96 (m, 2 H, 4-H), 1.76 (s, 3 H, 5-CH_3), 1.59–1.55 (m, 2 H, 3-H), 1.43–1.39 (m, 2 H, 2-H), 1.11 (s, 9 H, 9-CCH_3), 0.98 (s, 6 H, 1-CH_3);

^{13}C NMR δ 168.2 (s, 11-C), 163.4 (s, 9-C), 137.6 (s, 6-C), 133.5 (s, 7-C), 129.7 (s, 5-C), 128.8 (d, 8-C), 113.7 (d, 10-C), 51.0 (q, 11-OCH_3), 39.6 (t, 2-C), 37.0 (s, 9-CCH_3), 34.2 (s, 1-C), 33.0 (t, 4-C), 29.5 (q, 9-CCH_3), 28.8 (q, 1-CH_3), 21.4 (q, 5-CH_3), 19.2 (t, 3-C); UV (ethanol) λ_{max} (ε) 211 nm (9300); MS, *m/e* 290 (M^+); exact mass calcd for $C_{19}H_{30}O_2$ 290.2246, found 290.2245.

3-*tert*-Butyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadien-1-ol (6b). The reduction of 3.78 g (13 mmol) of **5b** in 20 mL of diethyl ether with a suspension of 0.57 g (15 mmol) of $LiAlH_4$ in 15 mL of diethyl ether was carried out as described for **6a**. After kugelrohr distillation (130 °C/0.005 mbar), 2.97 g of **6b** (11.3 mmol, 87%) was obtained as a colorless, viscous oil: IR (CCl_4) ν 3620, 3600–3200 cm^{-1}; ^1H NMR (300 MHz) δ 5.86 (d, 1 H, 8-H, $J_{7,8}$ = 16.2 Hz), 5.81 (d, 1 H, 7-H), 5.55 (t, 1 H, 10-H, $J_{10,11}$ = 6.4 Hz), 4.34 (d, 2 H, 11-H), 2.01 (m, 2 H, 4-H), 1.74 (s, 3 H, 5-CH_3), 1.64–1.58 (m, 2 H, 3-H), 1.48–1.45 (m, 2 H, 2-H), 1.10 (s, 9 H, 9-CCH_3), 1.02 (s, 6 H, 1-CH_3); ^{13}C NMR δ 151.0 (s, 9-C), 137.9 (s, 6-C), 132.8 (d, 7-C), 129.7 (d, 8-C), 128.8 (s, 5-C), 122.0 (d, 10-C), 61.2 (t, 11-C), 39.6 (t, 2-C), 35.8 (s, 9-CCh_3), 34.1 (s, 1-C), 32.9 (t, 4-C), 29.7 (q, 9-CCH_3), 28.9 (q, 1-CH_3), 21.8 (q, 5-CH_3), 19.3 (t, 3-C); UV (ethanol) λ_{max} (ε) 211 (6300), 247 nm (6900); MS, *m/e* 262 (M^+); exact mass calcd for $C_{18}H_{30}O$ 262.2297, found 262.2297.

3-*tert*-Butyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadienal (7b). The oxidation of 2.78 g (10.6 mmol) of **6b** in 200 mL of diethyl ether with 34.8 g (0.4 mol) of activated manganese dioxide was carried out as described for **7a** and yielded 1.98 g of **7b** (7.6 mmol, 72%, yellow oil) after purification by column chromatography: IR (CCl_4) ν 1670 cm^{-1}; ^1H NMR (300 MHz) δ 9.83 (d, 1 H, 11-H, $J_{10,11}$ = 7.4 Hz), 6.19 (d, 1 H, 7-H, $J_{7,8}$ = 15.6 Hz), 6.13 (d, 1 H, 8-H), 6.09 (d, 1 H, 10-H), 2.05 (m, 2 H, 4-H), 1.77 (s, 3 H, 5-CH_3), 1.65–1.61 (m, 2 H, 3-H), 1.50–1.46 (m, 2 H, 2-H), 1.17 (s, 9 H, 9-CCH_3), 1.04 (s, 6 H, 1-CH_3); ^{13}C NMR δ 193.6 (d, 11-C), 172.7 (s, 9-C), 139.1 (d, 7-C), 137.3 (s, 6-C), 131.5 (s, 5-C), 127.7 (d, 8-C), 125.9 (d, 10-C), 39.5 (t, 2-C), 36.8 (s, 9-CCH_3), 34.0 (s, 1-C), 33.0 (t, 4-C), 29.2 (q, 9-CCH_3), 28.9 (q, 1-CH_3), 21.8 (q, 5-CH_3), 19.1 (t, 3-C); UV (ethanol) λ_{max} (ε) 240 (9950), 294 nm (6300); MS, *m/e* 260 (M^+); exact mass calcd for $C_{18}H_{28}O$ 260.2140, found 260.2141.

19-Nor-9-*tert*-butylretinonitrile (9b). The Wittig–Horner reaction of 1.30 g (5 mmol) of **7b** in 5 mL of diethyl ether, 2.17 g (10 mmol) of phosphonate **8**[22] in 10 mL of THF and 0.4 g of sodium hydride (10 mmol, 60% in mineral oil) in 10 mL of THF was carried out as in the case of **9a**. After column chromatography 1.54 g of **9b** (4.8 mmol, 95%) was obtained as a yellow oil: IR (CCl_4) ν 2210 cm^{-1}; ^1H NMR (60 MHz) δ 7.1–6.0 (m, 3 H, 10-H, 11-H, 12-H), 5.95 (m, 2 H, 7-H, 8-H), 5.2–5.0 (m, 1 H, 14-H), 2.2–2.0 (m, 2 H, 4-H), 2.12 (s, 3 H, 13-CH_3), 1.78 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.15 (s, 9 H, 9-CCH_3), 1.07 (s, 6H, 1-CH_3); MS, *m/e* 323 (M^+); exact mass calcd for $C_{23}H_{33}N$ 323.2613, found 323.2615.

19-Nor-9-*tert*-butylretinal (10b). Aldehyde **10b** was obtained by reduction of 647 mg (2 mmol) of **9b** in 10 mL of hexane with 4.0 mL of DIBAH (4.0 mmol, 1.0 M solution in hexane) as described for **10a**. Purification of the crude product by column chromatography furnished 460 mg of **10b** (1.41 mmol, 70%) as a yellow oil. Product composition by HPLC analysis: 10% 9-*cis*,13-*cis*- and 90% 9-*cis*-**10b**. IR (CCl_4, 9-*cis*-**10b**): ν 1665 cm^{-1}. ^1H and ^{13}C NMR: see paragraph at the end of the paper about supplementary material. UV: see Table II. MS: *m/e* 326 (M^+); exact mass calcd for $C_{23}H_{34}O$ 326.2610, found 326.2609.

5-(2,6,6-Trimethylcyclohexen-1-yl)-3-(trimethylsilyl)-2,4-pentadienal (7c). To a solution of 2.27 g (15.5 mmol) of hexamethyldisilane in 8 mL of HMPTA was added 9.4 mL of MeLi (15.0 mmol, 1.6 M solution in diethyl ether) at 0 °C; the resulting red solution was stirred at this temperature for 15 min and treated with 30 mL of THF and 1.43 g (7.5 mmol) of copper(I) iodide. After another 20 min at 0 °C, the suspension was cooled to −30 °C and 1.50 g (6.5 mmol) of **4** in 15 mL of THF was added dropwise. The suspension was stirred at −30 °C for 2 h and quenched with 5 mL of methanol. Addition of water was followed by extractive workup, furnishing 1.96 g of crude ester **5c** as a red oil. The ester was dissolved in 20 mL of diethyl ether and added to a suspension of 285 mg (7.5 mmol) of $LiAlH_4$ in 20 mL of diethyl ether at −65 °C. The suspension was stirred for 2 h at −30 °C and hydrolyzed with 5 mL of saturated NH_4Cl solution. The precipitate formed was filtered off and washed with diethyl ether; drying of the filtrate and evaporation of the solvent yielded 1.72 g of crude alcohol **6c**. Oxidation to **7c** was accomplished by stirring a solution of **6c** in 50 mL of diethyl ether with 8.7 g (0.1 mol) of activated manganese dioxide for 17 h. After filtration, evaporation of the solvent, and column chromatography 480 mg of aldehyde **7c** (1.7 mmol, 27% from **4**) was obtained as a yellow oil: IR (CCl_4) ν 1670 cm^{-1}; ^1H NMR (400 MHz) δ 10.06 (d, 1 H, 11-H, $J_{10,11}$ = 7.8 Hz), 6.70 (d, 1 H, 8-H, $J_{7,8}$ = 15.9 Hz), 6.32 (d, 1 H, 7-H), 6.16 (d, 1 H, 10-H), 2.01 (m, 2 H, 4-H), 1.72 (s, 3 H, 5-CH_3), 1.63–1.56 (m, 2 H, 3-H), 1.48–1.42 (m, 2 H, 2-H), 1.01 (s, 6 H, 1-CH_3), 0.22 (s, 9 H, 9-$SiCH_3$); ^{13}C NMR δ 191.1 (d, 11-C), 164.5 (s, 9-C), 137.7 (s, 6-C), 137.2 (d, 7-C), 135.8 (d, 10-C), 131.7 (s, 5-C), 130.0 (d, 8-C), 39.5 (t, 2-C), 34.2 (s, 1-C), 33.1 (t, 4-C), 29.0 (q, 1-CH_3), 21.9 (q, 5-CH_3), 19.2 (t, 3-C), −1.2 (q, 9-$SiCH_3$); UV (ethanol) λ_{max} (ε) 211 (7900), 236 (8100), 323 nm (6000); MS, *m/e* 276 (M^+); exact mass calcd for $C_{17}H_{28}OSi$ 276.1909, found 276.1909.

19-Nor-9-(trimethylsilyl)retinonitrile (9c). The reaction of 80 mg of sodium hydride (2.0 mmol, 60% in mineral oil) in 2 mL of THF, 434 mg (2.0 mmol) of **8**[22] in 2 mL of THF, and 223 mg (0.81 mmol) of **7c** in 1 mL of diethyl ether was carried out as described for **9a** and yielded after column chromatography 150 mg of **9c** (0.44 mmol, 55%, yellow oil): IR (CCl_4) ν 2210 cm^{-1}; ^1H NMR (60 MHz) δ 7.3–5.9 (m, 5 H, 7-H, 8-H, 10-H, 11-H, 12-H), 5.2–5.1 (m, 1 H, 14-H), 2.2–2.0 (m, 2 H, 4-H), 2.15 (s, 3 H, 13-CH_3), 1.73 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.05 (s, 6 H, 1-CH_3), 0.22 (s, 9 H, 9-$SiCH_3$); MS, *m/e* 339 (M^+); exact mass calcd for $C_{22}H_{33}NSi$ 339.2382, found 339.2382.

19-Nor-9-(trimethylsilyl)retinal (10c). As described for **10a**, the reduction of 136 mg (0.4 mmol) of **9c** in 1 mL of hexane with 0.8 mL of DIBAH (0.8 mmol, 1.0 M solution in hexane) provided 75 mg of **10c** (0.22 mmol, 55%, red oil) after purification by column chromatography. The mixture of isomers was analyzed by HPLC and consisted of 16% 9-*cis*,13-*cis*- and 84% 9-*cis*-**10c**. IR (CCl_4, 9-*cis*-**10c**): ν 1670 cm^{-1}. ^1H and ^{13}C NMR: see the paragraph at the end of the paper about supplementary material. UV: see Table II. MS: *m/e* 342 (M^+); exact mass calcd for $C_{22}H_{34}OSi$ 342.2379, found 342.2410.

3-Methyl-1-(2,6,6-trimethylcyclohexen-1-yl)-1,3,5-octatrien-7-yne (12). To a solution of 38 mmol of lithium diisopropylamide (from 3.85 g diisopropylamine in 60 mL of THF and 23.8 mL of 1.6 M *n*-butyllithium in hexane) was added 9.30 g (36 mmol) of crude β-C_{18}-ketone **11**[31] in 20 mL of THF at −78 °C. The mixture was stirred at −78 °C for 1 h, and 6.56 g (38 mmol) of diethyl chlorophosphate was added. The mixture was allowed to warm to room temperature and was added to a solution of 80 mmol of lithium diisopropylamide (from. 8.10 g of diisopropylamine in 120 mL of THF and 50.0 mL of 1.6 M *n*-butyllithium in hexane) at −78 °C. The mixture was warmed to room temperature within 1 h and stirred for another 2 h. Water (50 mL) was added, and the major part of the solvent was removed by rotatory evaporation. The mixture was extracted with diethyl ether; the organic layers were washed with 1 N hydrochloric acid and water and dried. Evaporation of the solvent was followed by column chromatography providing 3.66 g of **12** (15.2 mmol, 42%) as a red oil: IR (CCl_4) ν 3310, 2100 cm^{-1}; ^1H NMR (60 MHz) δ 7.1–5.4 (m, 5 H, 7-H, 8-H, 10-H, 11-H, 12-H), 2.95 (d, 1 H, 14-H, $J_{12,14}$ = 2 Hz), 2.2–2.0 (m, 2 H, 4-H), 1.97 (s, 3 H, 9-CH_3), 1.70 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.03 (s, 6 H, 1-CH_3); MS, *m/e* 240 (M^+); exact mass calcd for $C_{18}H_{24}$ 240.1878, found 240.1880.

Methyl 20-Nor-13,14-didehydroretinoate (13). The reaction of 0.60 g (2.5 mmol) of **12** in 2 mL of diethyl ether with 1.5 mL of *n*-butyllithium (2.5 mmol, 1.7 M solution in hexane) and 0.33 g (3.5 mmol) of methyl chloroformate was carried out as described for the ester **4**, yielding 407 mg of **13** (1.36 mmol, 55%, red oil) after purification by column chromatography: IR (CCl_4) ν 2210, 1715 cm^{-1}; ^1H NMR (60 MHz) δ 7.3–5.4 (m, 5 H, 7-H, 8-H, 10-H, 11-H, 12-H), 3.72 (s, 3 H, 15-OCH_3), 2.2–2.0 (m, 2 H, 4-H), 2.00 (s, 3 H, 9-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.68 (s, 3 H, 5-CH_3), 1.02 (s, 6 H, 1-CH_3); MS, *m/e* 298 (M^+); exact mass calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1931.

Methyl 20-Nor-13-ethylretinoate (14a). A suspension of 500 mg (2.6 mmol) of copper(I) iodide in 4 mL of THF was treated with 4.2 mL of ethyllithium (5.2 mmol, 1.25 M solution in diethyl ether[17]) at 0 °C. A solution of 522 mg (1.75 mmol) of **13** in 4 mL

of THF was added at -78 °C and stirring was continued at this temperature for 2 h. Methanol (0.5 mL) was added, and the mixture was allowed to reach room temperature. Extractive workup, drying, evaporation of the solvent, and column chromatography yielded 510 mg of **14a** (1.55 mmol, 89%) as an orange oil: IR (CCl_4) ν 1720 cm^{-1}; ^1H NMR (60 MHz) δ 7.9–6.0 (m, 5 H, 7-H, 8-H, 10-H, 11-H, 12-H), 5.58 (s, 1 H, 14-H), 3.65 (s, 3 H, 15-OCH_3), 2.45 (q, 2 H, 13-CH_2, J = 7 Hz), 2.2–2.0 (m, 2 H, 4-H), 1.98 (s, 3 H, 9-CH_3), 1.70 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.17 (t, 3 H, 13-CCH_3), 1.05 (s, 6 H, 1-CH_3); MS, m/e 328 (M^+); exact mass calcd for $C_{22}H_{32}O_2$ 328.2402, found 328.2405.

20-Nor-13-ethylretinal (15a). To 68 mg (1.8 mmol) of $LiAlH_4$ in 5 mL of diethyl ether was added 510 mg (1.55 mmol) of **14a** in 5 mL of diethyl ether at -65 °C. The mixture was stirred at -30 °C for 2 h and hydrolyzed with 1 mL of saturated NH_4Cl solution. The precipitate was filtered off and washed with diethyl ether. The crude alcohol obtained after drying of the filtrate and evaporation of the solvent was dissolved in 40 mL of diethyl ether, and 5.2 g (0.06 mol) of activated manganese dioxide was added. After the mixture had been stirred for 15 h, the manganese dioxide was removed by filtration, and the solvent was evaporated. Purification of the crude aldehyde by column chromatography provided 225 mg of **15a** (0.75 mmol, 49%) as a yellow oil. The product was analyzed by HPLC and consisted out of 55% 13-*cis*- and 45% 9-*cis*,13-*cis*-**15a**: IR (CCl_4, 13-*cis*-**15a**): ν 1670 cm^{-1}. ^1H and ^{13}C NMR: see paragraph at the end of the paper about supplementary material. UV: see Table II. MS: m/e 298 (M^+); exact mass calcd for $C_{21}H_{30}O$ 298.2297, found 298.2300.

Methyl 20-Nor-13-*tert*-butylretinoate (14b). A suspension of 434 mg (2.28 mmol) of copper(I) iodide in 4 mL of THF was treated with 2.9 mL of *tert*-butyllithium (4.55 mmol, 15% solution in pentane) at -30 °C. After addition of 522 mg (1.75 mmol) of **13** in 4 mL of THF at -78 °C and stirring at this temperature for 2 h, 0.5 mL of methanol was added. Workup was carried out as described for **14a** and furnished 483 mg of **14b** (1.35 mmol, 77%) as an orange oil: IR (CCl_4) ν 1725 cm^{-1}; ^1H NMR (60 MHz) δ 7.0–6.0 (m, 5 H, 7-H, 8-H, 10-H, 11-H, 12-H), 5.83 and 5.67 (2 × s, 1 H, 14-H), 3.65 and 3.60 (2 × s, 3 H, 15-OCH_3), 2.2–2.0 (m, 2 H, 4-H), 1.97 (s, 3 H, 9-CH_3), 1.70 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 2 H, 2-H, 3-H), 1.23 and 1.20 (2 × s, 9 H, 13-CCH_3), 1.03 (s, 6 H, 1-CH_3); MS, m/e 356 (M^+). Exact mass calcd for $C_{24}H_{36}O_2$ 356.2715, found 356.2707.

20-Nor-13-*tert*-butylretinal (15b). The reduction of 483 mg (1.35 mmol) of **14b** in 5 mL of diethyl ether with 61 mg (1.6 mmol) of $LiAlH_4$ in 5 mL of diethyl ether and the reoxidation with 4.3 g (0.05 mol) of activated manganese dioxide was carried out as described for **15a**, yielding 260 mg of **15b** (0.80 mmol, 59%) as a yellow oil. The composition of the product mixture was determined by HPLC: 33% 9-*cis*,13-*cis*- and 67% 13-*cis*-**15b**; IR (CCl_4, 13-*cis*-**15b**) ν 1670 cm^{-1}. ^1H and ^{13}C NMR: see paragraph at the end of the paper about supplementary material. UV: see Table II. MS: m/e 326 (M^+); exact mass calcd for $C_{23}H_{34}O$ 326.2610, found 326.2622.

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Supplementary Material Available: Tables of ^1H and ^{13}C NMR data for compounds **10** and **15** (6 pages). Ordering information is given on any current masthead page.

Chemistry of N-Heterocyclic Sulfur Compounds. Reaction of 2,5-Dimercapto-1,3,4-thiadiazoles with 1,ω-Dibromoalkanes. Synthesis of Tetrathia[(*n* + 2).(*n* + 2)](2,5)-1,3,4-thiadiazolophanes and Dithia[(*n* + 1).(*n* + 1)](3,5)-1,3,4-thiadiazolinophanedithiones

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The base-catalyzed reaction of 2,5-dimercapto-1,3,4-thiadiazole (**1**) with 1,ω-dibromoalkanes $Br(CH_2)_nBr$ (n = 1–4) has been investigated. Model experiments on the alkylation of 2-mercapto-5-(methylthio)-1,3,4-thiadiazole (**3**) with 1,ω-dibromoalkanes and 2,5-bis[(chloroalkyl)thio]-1,3,4-thiadiazoles, as well as on the dialkylation of **1** with 2-[(chloroalkyl)thio]-5-(methylthio)-1,3,4-thiadiazoles, have shown that both **3** and **1** undergo regioselective S-alkylation under basic conditions. However, the heterocyclization of **1** with 1,ω-dibromoalkanes and 2 equiv of KOH, carried out in EtOH under high dilution conditions, not only gave the expected S,S-bridgehead 2:2 macrocycles **2a** (m = 1; n = 1, 2, 4), i.e., tetrathia[(n + 2).(n + 2)](2,5)-1,3,4-thiadiazoles, but also the S,N-bridgehead 2:2 macrocycles **2b** (m = 1; n = 2, 3), i.e., dithia[(n + 1).(n + 1)](3,5)-1,3,4-thiadiazolinophanedithiones. Furthermore, the high-dilution reaction of **1** with CH_2Br_2 and triethylamine gave 1,3,9,11,17,19-hexathia[3.3.3](2,5)-1,3,4-thiadiazolinophane (**19**) (**2a**: m = 2; n = 1), while the use of 1 equiv of KOH under moderate dilution resulted in the formation of the macrocyclic isomer 1,8,15-trithia[2.2.2](3,5)-1,3,4-thiadiazolinophane-4,11,18-trithione (**20**) (**2b**: m = 2; n = 1). The product distribution appears to be strongly dependent on the experimental conditions used, the nature and amount of base, the length of the dibromide, and its strength as an electrophilic agent. Several competing mechanisms have been ascertained to occur in the base-catalyzed heterocyclization of **1** with 1,ω-dibromoalkanes. The proposed reaction pathways gain support from the study of appropriate model reactions and from the isolation and identification of the involved key intermediates. ^{13}C NMR spectroscopy has been extensively used to firmly establish the structures of the compounds obtained.

In the light of potential biological[1] and analytical[2,3] interest in disubstituted 1,3,4-thiadiazoles, as well as the limited examples of 1,3,4-thiadiazole inclusion in a macrocyclic framework,[4] recently we described the synthesis

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