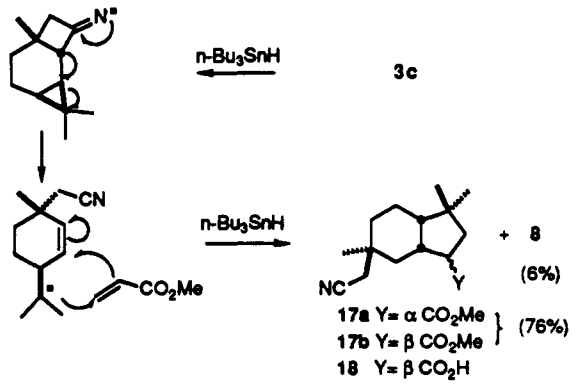

Figure 3.

markably *regiospecific*[9] cleavage of the cyclopropyl ring (Figure 2).[12] Absolute kinetic data on carbon to carbon 1,5-migration of a hydrogen atom are rather scanty,[13a] and those involving saturated carbons have generally been considered as too sluggish and unselective for synthetic purposes.[13,14] Evidently, in the light of the present results, these processes certainly embody a far greater synthetic potential than has hitherto been appreciated.

The intermediate carbon radical may be captured by an external electrophilic olefin. Thus, in the presence of methyl acrylate, the reaction of sulphenylimine **3a** with tributylstannane gives the *trans-substituted* compound **16** in 65–70% yield.[15] Under the same conditions, sulphenylimine **3c** afforded, via the sequence displayed in Figure 3, bicyclic compound **17** as a mixture of epimers (α/β 3:7) in 76% yield, and only a small amount of **8** (6%). Epimerization (K_2CO_3/MeOH, 20 °C, 48 h) and saponification furnished acid **18** (98%) as a sole isomer.

In view of the fact that cyclobutanones are readily available by a variety of methods, some of which are regio-, stereo-, and even enantioselective,[16] we feel that this novel methodology holds considerable synthetic promise.

Acknowledgment. We thank Prof. J.-Y. Lallemand for help and encouragement and Rhône-Poulenc Agrochimie for generous financial support (to E.F.).

Supplementary Material Available: Experimental procedure and spectral data for **6–10**, **13**, **16**, **17a**, **17b**, and **18** (2 pages). Ordering information is given on any current masthead page.

(12) The geometric disposition in the transition state of the atoms involved in the migration of the hydrogen is not favorable for a stabilizing interaction with the cyclopropyl ring which, in any case, is relatively small for radicals (3–4 kcal/mol); see: (a) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809, and references therein. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 169. (c) Wilcox, C. F.; Loew, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1973**, *95*, 8192.

(13) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1. (b) Choi, J. K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959. (c) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409. (d) Winkler, J. D.; Sridar, V.; Rubo, L.; Hey, J. P.; Haddad, N. *J. Org. Chem.* **1989**, *54*, 3004, and references cited therein. (e) For a rare example of an efficient 1,5 hydrogen atom migration involving saturated carbons, see: Boivin, J.; Da Silva, E.; Ourisson, G., Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 2501.

(14) Useful carbon to carbon translocations of radical centers are normally triggered by a highly energetic (vinylic or aromatic) initial carbon radical so that the migration becomes exothermic and irreversible: see: (a) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (b) Lathbury, D. C.; Parsons, P. J.; Pinto, I. J. *J. Chem. Soc., Chem. Commun.* **1988**, 81. (c) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878. (d) See also refs 5a,b.

(15) It is worth noting that a base-catalyzed Dieckmann-type cyclization between the nitrile and ester-containing chains would lead to a six-membered ring *trans-fused* to the original cyclopentene unit in **1a**.

(16) See, inter alia: (a) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797, and references therein. (b) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793. (c) Moore, H. W.; Gheorghiu, M. *Chem. Soc. Rev.* **1981**, *10*, 289. (d) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949. (e) For a recent practical asymmetric synthesis of cyclobutanones, see: Chen, L.-Y.; Ghosez, L. *Tetrahedron Lett.* **1990**, *31*, 4467.

Synthesis of the Highly Oxygenated Ergostane Type Steroid (+)-Withanolide E

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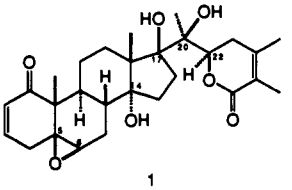
Received November 2, 1990

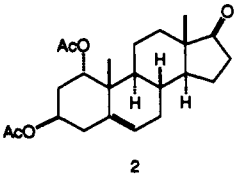
Withanolide E (**1**)[1] belongs to a group of highly oxygenated steroid-based δ lactones isolated from *Withania somnifera* Dun. chemotype III (Solaneceae) found in Israel and possesses a rich array of pharmacological properties including insect antifeedant, antifungal, and antitumor activity similar to the biological properties associated with cardenolides and bufadienolides.[2] It



1

is interesting to note that withanolide E, which possesses 10 contiguous chiral centers of which six are oxygenated, differs from cardenolides and bufadienolides by (1) the unusual C(17) α arrangement of the side chain and (2) the CD trans ring fusion bearing an α hydroxyl group at C(14).[3] We detail below the synthesis of (+)-withanolide E, which constitutes the first reported synthesis of a withanolide of chemotype III.[4]

Our strategy for elaboration of (+)-withanolide E involves a hetero Diels–Alder reaction[6] between steroidal dienol acetate **3** and benzyl nitrosoformate which allows for the introduction of an α-hydroxyl group into the C(14) position. The requisite dienol



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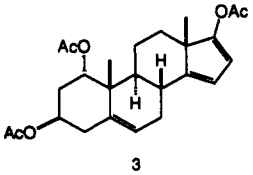

3

acetate **3** was prepared in straightforward fashion from the known steroidal diacetate **2**.[7] Conversion [TMSI, $(TMS)_2NH$, Et_3N, $ClCH_2CH_2Cl$, −23 °C, 45 min] of **2** into its corresponding silyl enol ether via a modification of the Miller procedure[8] followed by a Saegusa reaction [$Pd(OAc)_2$, K_2CO_3, CH_3CN, 12 h][9] and subsequent exposure to refluxing isopropenyl acetate containing *p*-toluenesulfonic acid gave rise to **3**, $[\alpha]_D$ +104.8° (*c* 3.88, $CHCl_3$) in 86% overall yield. Treatment (CH_2Cl_2, 0 °C, 20 min) of **3** with benzyl nitrosoformate, generated in situ by oxidation of benzyl *N*-hydroxycarbamate with tetrabutylammonium periodate, afforded in nearly quantitative yield the isomeric cycloadducts **4**

(1) Lavie, D.; Kirson, I.; Glotter, E.; Rabinovich, D.; Shakked, Z. *J. Chem. Soc., Chem. Commun.* **1972**, 877. Glotter, E.; Abraham, A.; Günzberg, G. J.; Kirson, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 341.

(2) Cassady, J. M.; Suffness, M. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; p 201. Ascher, K. R. S.; Nemny, N. E.; Eliyahu, M.; Kirson, I.; Abraham, A.; Glotter, E. *Experientia* **1980**, *36*, 998. Ascher, K. R. S.; Schmutteres, H.; Glotter, E.; Kirson, I. *Phytoparasitica* **1981**, *9*, 197. Abraham, A.; Kirson, I.; Lavie, D.; Glotter, E. *Phytochemistry* **1975**, *14*, 189.

(3) Note that the withanolides of chemotypes I and II possess the natural C(17) β orientation typical of cardenolides and bufadienolides. For a review on withanolides, see: Kirson, I.; Glotter, E. *J. Nat. Prod.* **1981**, *44*, 633.

(4) Withanolides of chemotypes I and II have been previously synthesized;[5] however, they lack the presence of hydroxyl groups at C(14), C(17), and, in some cases, C(20).

(5) Hirayama, M.; Gamoh, K.; Ikekawa, N. *J. Am. Chem. Soc.* **1982**, *104*, 3735. Hirayama, M.; Gamoh, K.; Ikekawa, N. *Tetrahedron Lett.* **1982**, *23*, 4725. Gamoh, K.; Hirayama, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 449.

(6) Cf.: Kirsch, G.; Golde, R.; Neef, G. *Tetrahedron Lett.* **1989**, *30*, 4497.

(7) Fürst, A.; Labler, L.; Meier, W. *Helv. Chim. Acta* **1981**, *64*, 1870.

(8) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.

(9) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

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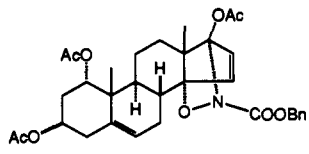
and **5** in a 2:1 ratio. Upon brief exposure (20 min) to refluxing



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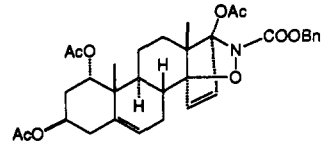
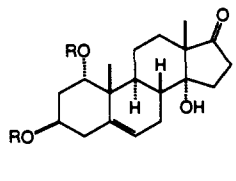


5

toluene, the minor adduct **5** was transformed into the desired α adduct **4**, $[\alpha]_D$ −39.6° (*c* 2.79, $CHCl_3$). The overall yield for the formation of **4** was 85%. The transformation of **4** into the C(14) α-hydroxy steroid **6** (R = OAc), mp 250–252 °C, was achieved via a two-step sequence [(1) H_2, 5% Pd–$BaSO_4$, EtOH, 3 h; (2) $CuCl_2 \cdot 2H_2O$, H_2O–THF (1:5), 4 h] in 79% overall yield. Hydrolysis (5% KOH, MeOH, reflux, 2 h) provided in quantitative yield triol **6** (R = H).



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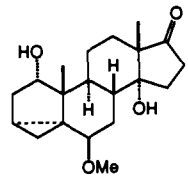
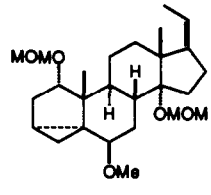


7

Having secured the stereochemistry at C(14), attention was focused on the C(17) β-oriented hydroxyl group. Prior to manipulation of the carbonyl group at C(17), ring A was transformed via a four-step sequence [(1) TsCl, pyr, 12 h; (2) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C, 30 min; (3) MeOH, KOAc, reflux, 12 h; (4) Bu_4NF, THF, 4 days] into the 3,5-cyclosteroid **7**, mp 200–201 °C, in 50% overall yield. Whereas introduction of a C(17) β-hydroxyl group might appear to be a straightforward proposition, all attempts to add a variety of nucleophiles to C(17) gave rise to the undesired configuration at C(17). This was a problem whether the C(14) hydroxyl group was protected or not. The difficulties encountered above were circumvented by utilizing the (17*Z*)-ethylidene steroid **8**, which was prepared in 85% overall yield by treatment of **7** with ethylidenetriphenylphosphorane in tetrahydrofuran followed by protection (MOMCl, *i*-Pr_2NEt, dioxane, 80 °C, sealed tube, 24 h) of the hydroxyl groups at C(1) and C(14) as MOM ethers. Exposure (24 h) of **8** to osmium



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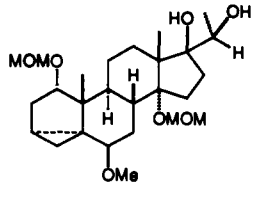

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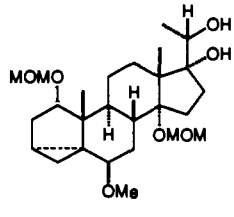
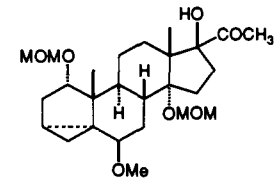


10

tetraoxide in pyridine gave rise in 80% yield to a 1.4:1 mixture of glycols **9** and **10** which could be readily separated. Oxidation (TFAA, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h) of **9** gave rise to the crystalline 3,5-cyclosteroid **11**, mp 134–135 °C, in 89% yield.

With the stereochemistry at C(17) established, our efforts were directed at C(20). Models suggested that addition of vinyllithium to ketone **11** would be controlled by chelation of the lithium alkoxide with the C(20) keto group (cf. structure i) giving rise to the desired configuration at C(20). Indeed treatment of ketone **11** with excess vinyllithium in tetrahydrofuran at −78 °C for 1



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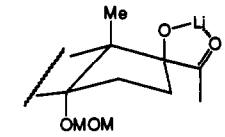
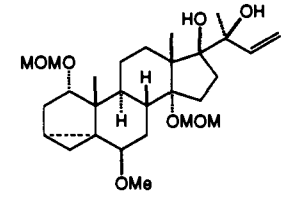
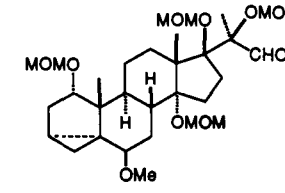


i

h led in 97% yield to the formation of a single crystalline diastereomer, mp 144–146 °C, possessing the desired stereochemistry (cf. compound **12**) at C(20). Protection (MOMCl, *i*-Pr_2NEt, dioxane, 90 °C, sealed tube, 24 h, 65%) of the hydroxyls at C(17) and C(20) in **12** followed by cleavage (O_3, MeOH, −100 °C; Me_2S, 30 min) of the terminal olefin afforded aldehyde **13**, $[\alpha]_{436}$ +92.1° (*c* 1.19, $CHCl_3$), in 70% yield.

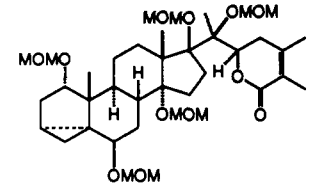


12



13

The availability of aldehyde **13** set the stage for elaboration of the stereochemistry at C(22). Treatment [−78 °C → room temperature (1.5 h)] of aldehyde **13** with the lithium enolate derived from ethyl α,β-dimethylcrotonate (LDA, THF, HMPA) provided exclusively δ lactone **14** bearing the desired configuration at C(22). That the stereochemistry of the hydroxyl-bearing



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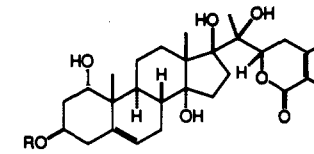
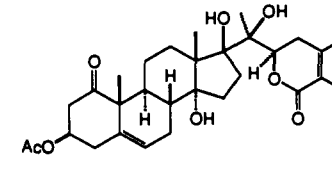


15

carbons at C(14), C(17), C(20), and C(22) was correct, as depicted in structure **14**, was unambiguously established by single-crystal X-ray analysis of the fully deprotected pentaol **15** (R = H),[10] mp 273–274 °C, obtained by exposure (36 h) of **14** to 2 M aqueous sulfuric acid–dioxane (3:10).

Completion of the synthesis of withanolide E necessitated elaboration of the AB ring system possessing a β-oriented epoxide at C(5), C(6). Toward this end pentaol **15** (R = H) was selectively acetylated (Ac_2O, DMAP, pyr, 15 h) at C(3), giving rise in 72% yield to acetate **15** (R = Ac). Swern oxidation at C(1) provided in 78% yield the C(1) ketone **16**, which upon treatment (40 min)



16

with 1,5-diazabicyclo[4.3.0]non-5-ene in methylene chloride and subsequent epoxidation (MCPBA, $NaHCO_3$, CH_2Cl_2, 18 h) afforded, in 71% overall yield from **16**, (+)-withanolide E (**1**) [mp 165–166 °C, $[\alpha]_D$ +101.5° (*c* 0.15, $CHCl_3$)], whose physical and spectral properties were found to be identical with those of an

(10) Compound **15** (R = H) crystallizes in space group $P2_12_12_1$ with cell dimensions of a = 12.309 (8) Å, b = 22.861 (16) Å, and c = 11.566 (8) Å; V = 3254.50 Å^3, ρ_{calcd} = 1.489 g cm^{-3} (Z = 4). A total of 2592 reflections were measured, of which 1713 were determined to be observable, $F_o > 2.33\sigma(F)$. All atoms, including hydrogens, were located and refined to final residuals of $R(F)$ = 0.0963 and $R_w(F)$ = 0.0906.

authentic sample of **1** kindly provided by Professor Glotter.

Acknowledgment. Generous support for this work from the National Cancer Institute, National Institutes of Health (Grant CA 28865), is gratefully acknowledged. We thank G. D. Searle and Co. for a generous gift of steroid diacetate **2** and Professor Erwin Glotter of the Hebrew University of Jerusalem for an authentic sample of withanolide E. We are grateful to Dr. John C. Huffman for carrying out the X-ray crystallographic analysis, Dr. R. J. Cooke for experimental assistance during the early stages of the synthesis, and Dr. Günther Neef (Schering AG, Berlin) for unpublished experimental details.

Fluorine Substituent Effects on Thermal Isomerizations: A New Thermal Reaction of 1,3,5-Hexatrienes

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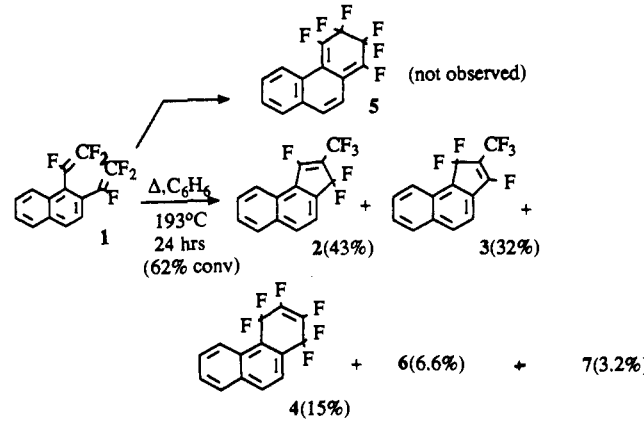
Received September 20, 1990

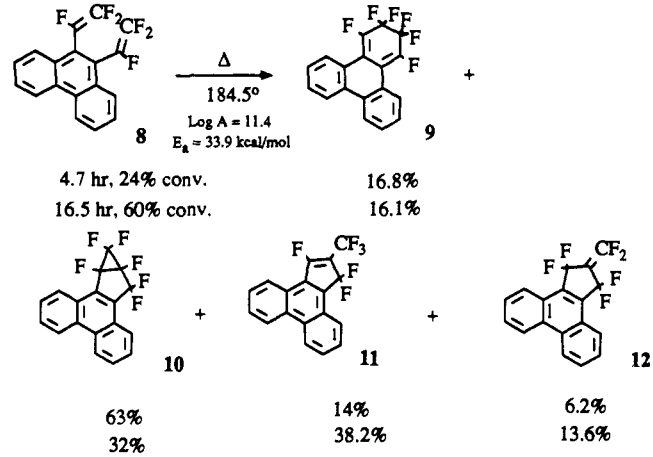
Fluorine substituents have been observed to have a remarkable effect upon the rate and stereochemical outcome of the butadiene–cyclobutene thermal conrotatory 4π-electron electrocyclic interconversion.[1] The substituent effects observed in this system[2] and in other pericyclic systems[3,4] have enhanced one's understanding of the mechanisms of such reactions,[2,5] such that only a small probable effect of fluorine substituents was predicted[6] for the related 6π-electron system, i.e., the disrotatory 1,3,5-hexatriene–1,3-cyclohexadiene conversion.

In an attempt to probe this system, a strategy was devised which would utilize the thermolysis of 1,2-bis(trifluorovinyl)naphthalene (**1**).[7,8] In thermal isomerizations, divinyl aromatics had been observed to undergo electrocyclic reactions in a manner similar to their acyclic analogues,[9] and the probable effect of the fluorine substituents upon the thermodynamics of this reaction provided us with the prospect of a fruitful system for kinetic and thermodynamic analysis. In this paper initial results from these studies are reported, wherein the expected normal electrocyclic process is seen to play but a minor role, with a new and virtually unprecedented thermal isomerization being seen to dominate the thermal chemistry of this and a related system.

When **1** was heated in benzene at 193 °C for 24 h, three major products could be isolated and characterized.[10] None of the expected electrocyclic product **5** could be detected.



Because of the more favorable thermodynamics of the system, the thermolysis of 9,10-bis(trifluorovinyl)phenanthrene (**8**)[12] was examined, and it provided greater insight into this chemistry. While a small amount of electrocyclic product **9** was detected in this system,[13] again the *major* observed reaction was that which had been observed for **1**. After one half-life, the major product was **11**, but by examination of the early stages of the reaction it became clear that **11** was being formed from an intermediate (**10**) which apparently was itself the major direct product of the thermolysis of **8**. Indeed, at 24% conversion of **8**, 63% of the product mixture was **10**.



Bicyclo[3.1.0]hex-2-enes such as **10** have, of course, been observed as major products in the *photochemistry* of acyclic 1,3,5-hexatrienes[14] as well as of divinyl aromatics,[15] but are virtually unprecedented products in thermal reactions of such substrates.[16] The structure of **10** was confirmed spectroscopically,[10] and it was indeed found also to be the major product from photolysis of **8**. Thermolysis of **10** also proceeded smoothly (k_{10}/k_8 = 1.94 at 180 °C), and it was thus demonstrated that **10** was the precursor of both **11** (38%) and **12** (62%), but not of **9**. Therefore, it would appear that in the thermolysis of **8** a competition between the expected, normal electrocyclic process to form orthoquinoid species **9** and a new thermal process which leads to the major bicyclo[3.1.0]hexene product **10** is being observed.

(1) Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. L.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1987**, *109*, 219 and references therein.
(2) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.
(3) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.
(4) Dolbier, W. R., Jr.; Phanstiel, O., IV. *Tetrahedral Lett.* **1988**, *29*, 53.
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(12) Synthesized by an unusual bis Pd(0)-catalyzed coupling of (trifluorovinyl)zinc with 9-iodo-10-nitrophenanthrene.
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