A total synthesis of estrone based on a novel cascade of radical cyclizations

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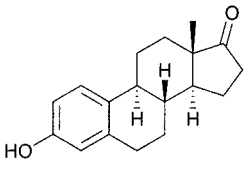
Two conceptually different and novel radical-mediated cascade reactions leading to a total synthesis of the steroid (±)-estrone 1 and to a synthesis of 14-epiestrone 40 are described. Treatment of the iododienynone 23 with Bu_3SnH/2,2′-azobis(isobutyronitrile) (AIBN) triggers a 13-*endo*-dig radical macrocyclization followed by two sequential radical transannulation reactions leading to the crystalline estrane 24 in 50% yield. The x-ray crystal structure of 24 established its *trans*, *syn*, stereochemistry. Transposition of the enone functionality in 24 next led to 38, which was then converted into 39 by reductive methylation. Deprotection of the methyl ether 39 finally gave 14-epiestone 40. When the substituted iodovinylcyclopropane 55 was treated similarly with Bu_3SnH/AIBN, the resulting radical center underwent a different sequence of cascade macrocyclization-transannulation reactions producing the *trans*, *anti*, *trans* estrane 56 in 12% overall yield. Oxidation of 56, using CrO_3-H_2SO_4 next led to the cyclopentanone 57, which, on deprotection using BBr_3 gave (±)-estrone 1. A number of alternative substituted iodopolyenynones and iodovinylcyclopropanes, i.e., 8a, 8b, 33, 49a, and 49b, underwent similar radical-mediated cascade cyclizations leading to other estranes, i.e., 21a, 21b, 35, and 50, and, in one case, to the 6,6,5,6-tetracycle 51, in variable overall yields. The structures and stereochemistries of several estranes were established by using x-ray crystal structure measurements in combination with analysis of their NMR spectroscopic data and correlation with literature precedent.

Since the synthesis of the female sex hormone estrone **1** by Anner and Miescher in 1948 (1), and the syntheses of nonaromatic steroids, such as cortisone **2** and aldosterone **3** during the 1950s, a plethora of ingenious designs have been explored to synthesize members of the steroid family of natural products. Prominent among the methods that have been developed are those based on Diels–Alder reactions (2–12), transition metal-catalyzed cyclizations of enynes and triynes (13–16), and biogenetic–type electrophilic cyclizations of polyene precursors (17–21).



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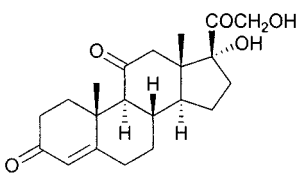

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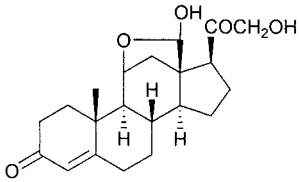

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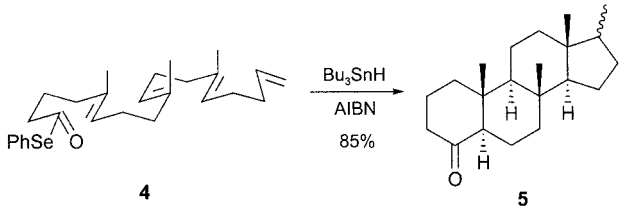
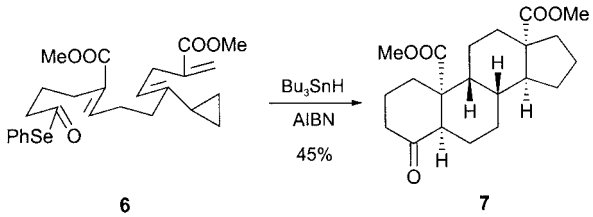
Over the past 10 years, we (22–26) and others (27–38) have examined the scope of a variety of cascade radical-mediated processes to elaborate steroids and other polycyclic ring systems. Thus, we have already described an approach to steroids based on consecutive 6-*endo*-trig (ref. 39 and references therein) and sequential transannular (40) radical cyclizations from appropriate polyene selenyl ester precursors, illustrated in the conversions **4** → **5** and **6** → **7**, respectively.



4 **5**



6 **7**

We have now extended our studies and examined a different approach to estrone **1** and estranes, whereby the nonaromatic tricyclic B,C,D ring system is produced in a single step by radical-mediated macrocyclizations in tandem with consecutive transannulations from an appropriate *ortho*-disubstituted arylpolyene precursor.

These approaches to estranes are captured in a retrosynthetic manner in Scheme 1. Thus, in one approach, we have studied the sequential 13-*endo*-trig macrocyclization/transannulation radical cascade from the iodopolyene precursor **8**, and in the second approach, we have explored the alternative radical macrocyclization/transannulation cascade from the iodovinylcyclopropane **10** (Scheme 2). These investigations are brought together in this article and have culminated in a conceptually distinct total synthesis of estrone **1**.

It is well established that electron-deficient alkenes (and alkynes), e.g., **8**, act as efficient radical acceptor groups, or electrophores, in macrocyclizations involving nucleophilic car-

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Abbreviations: AIBN, 2,2′-azobis(isobutyronitrile); THF, tetrahydrofuran; TBS, *t*-butyldimethylsilyl.

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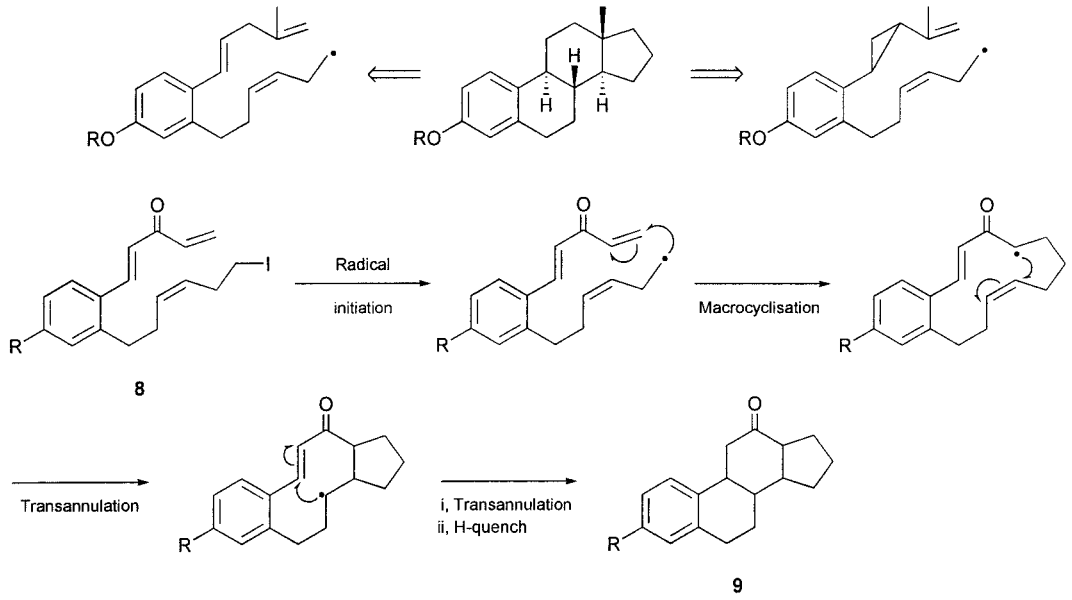


Scheme 1. Retrosynthesis analysis.

bon-centered radicals (41–45). There are also many illustrations of the applications of radical-mediated transannulations in the current literature (46–48). The similarity in the chemistries of alkenes and cyclopropanes is also well known, as is the propensity for cyclopropylmethyl radicals to undergo irreversible conversions into but-3-enyl radicals, i.e., **11** → **12**. Clearly, the pathways followed by the planned radical cascades **8** → **9** and **10** → **13** will depend on a range of features, including the stereochemistries of the alkenes and cyclopropanes, the conformational preferences of the large and medium ring intermediates and, of course, competing side reactions involving radical quenching and hydrogen abstraction processes.

Experimental Methods

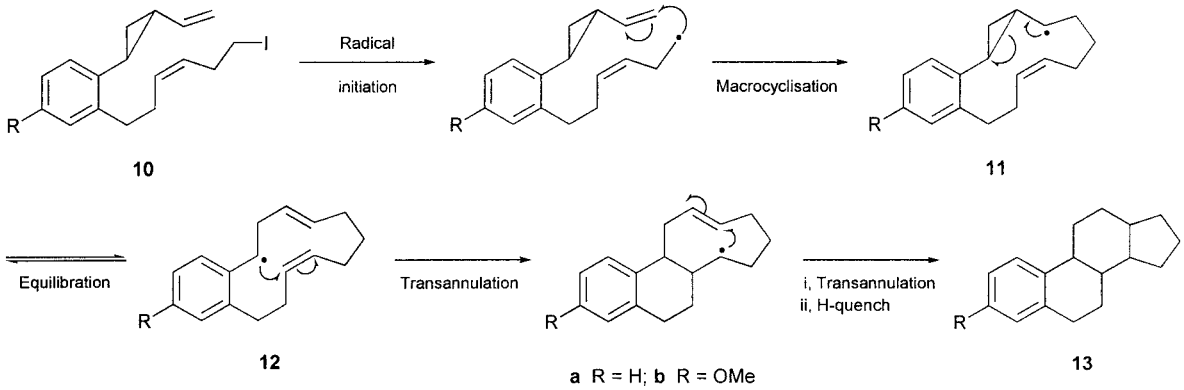
For general details, see ref. 49. Specific details of the synthesis and characterizations of all of the compounds researched in this article can be found in *Supporting Methods*, which is published as supporting information on the PNAS web site.

Results and Discussion

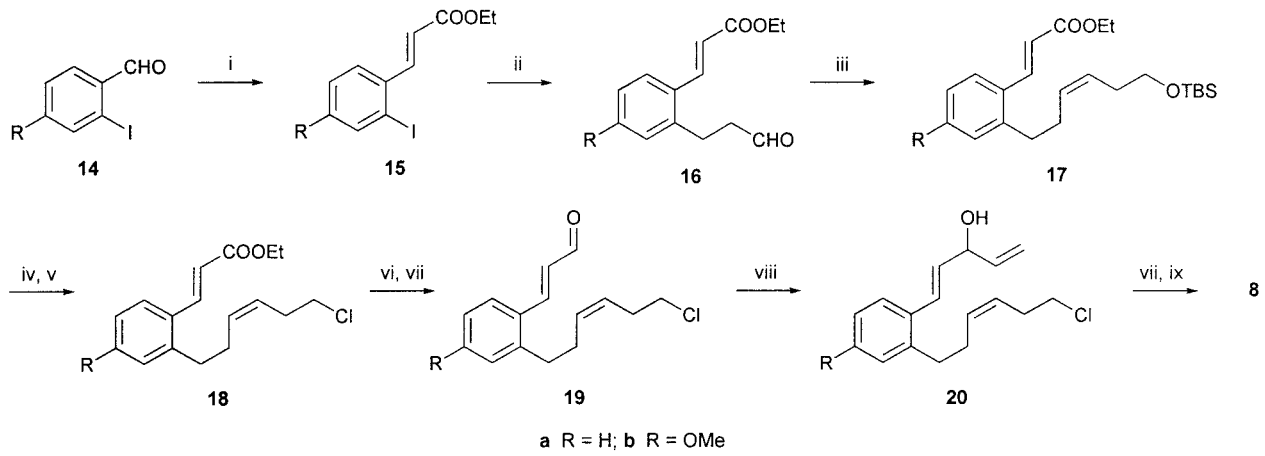
We began our investigation of the radical macrocyclization/transannulation cascade **8** → **9** by synthesizing the appropriate iodopolyenone starting materials **8a** and **8b**. These syntheses were achieved in rapid fashion from known *o*-iodobenzaldehydes **14** after (*i*) Wadsworth–Emmons olefination reactions to the corresponding cinnamate esters **15**; (*ii*) Heck reactions (50) between the iodoaromatics **15** and propen-1-ol, producing the corresponding arylpropanals **16** (Scheme 3); (*iii*) *Z*-selective Wittig reactions of **16** with triphenyl(*t*-butylsilyloxy)propyltriphenylphosphonium iodide leading to **17**; (*iv*) functional group interconversions via **18** ultimately producing **19**; (*v*) Grignard reactions between **19** and the appropriate organomagnesium reagent, and oxidation of the resulting secondary alcohol **20** to the corresponding dienone; and finally, (*vi*) chloride–iodide interchange producing the iodopolyenones **8**.

When solutions of the iodotrienones **8a** and **8b** in benzene were treated separately with Bu_3SnH and catalytic 2,2′-azobis(isobutyronitrile) (AIBN) over 6 h under high-dilution conditions, work-up and purification by chromatography led to the isolation of approximately equal amounts of two crystalline 12-ketosteroid products, from each reaction, in combined yields of ≈50% (for preliminary studies, see ref. 51). Crystals of one of the products resulting from cyclization of **8a** were suitable for x-ray analysis, which showed that the 12-ketosteroid **21a** had the *cis, anti, trans* stereochemistry drawn.

A close correlation between the NMR spectroscopic data recorded for **21a** and the data measured for the major tetracyclic

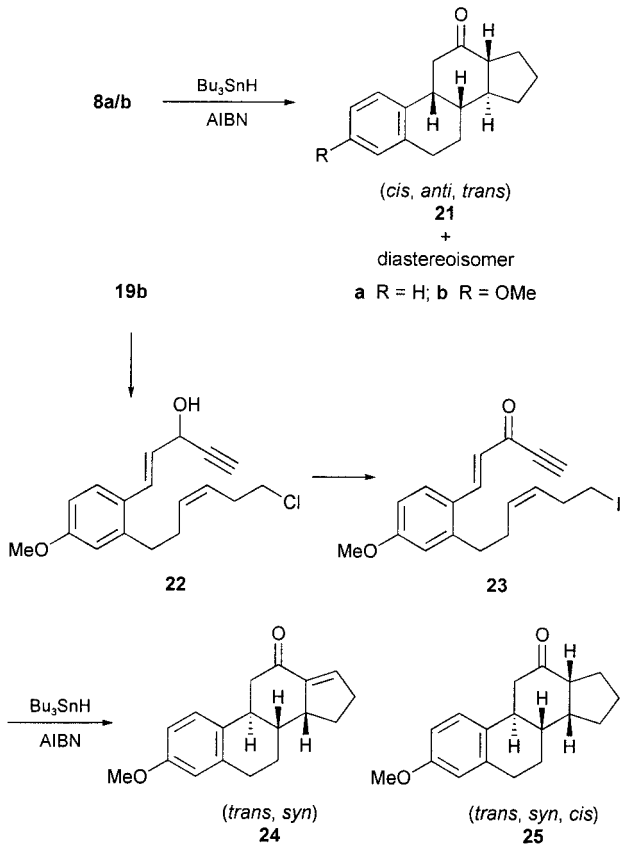


Scheme 2. Radical cascade reactions leading to estranes.



Scheme 3. (*i*) $EtO_2CCH_2PO(OEt)_2$, BuLi, tetrahydrofuran (THF), 72% yield; (*ii*) $CH_2{=}CHCH_2OH$, $Pd(OAc)_2$, *n*-Bu_4NCl, dimethylformamide (DMF), 62–53% yield; (*iii*) $IPh_3P(CH_2)_3OTBS$ (TBS, *t*-butyldimethylsilyl), potassium hexamethyldisilazane (KHMDS), THF, 80% yield; (*iv*) tetrabutylammonium fluoride (TBAF), THF, 90% yield; (*v*) *N*-chlorosuccinimide (NCS), PPh_3, Cl_2CH_2, 84–69% yield; (*vi*) iBu_2AlH, Cl_2CH_2, 81–78% yield; (*vii*) pyridinium dichromate (PDC), Cl_2CH_2, 92–62% yield; (*viii*) $H_2C{=}CHMgBr$, THF, 88–62% yield; (*ix*) NaI, $MeCOCH_2Me$, 92–87% yield.

product resulting from the methoxy derivative **8b** was obtained, thereby demonstrating that this steroid, likewise, had the same *cis*, *anti*, *trans* geometry, i.e., **21b**. Attempts to grow crystals of the other diastereoisomers of the 12-ketosteroids produced from **8a**/**b**, for x-ray studies proved to be fruitless. Therefore, their relative stereochemistries remain unresolved.



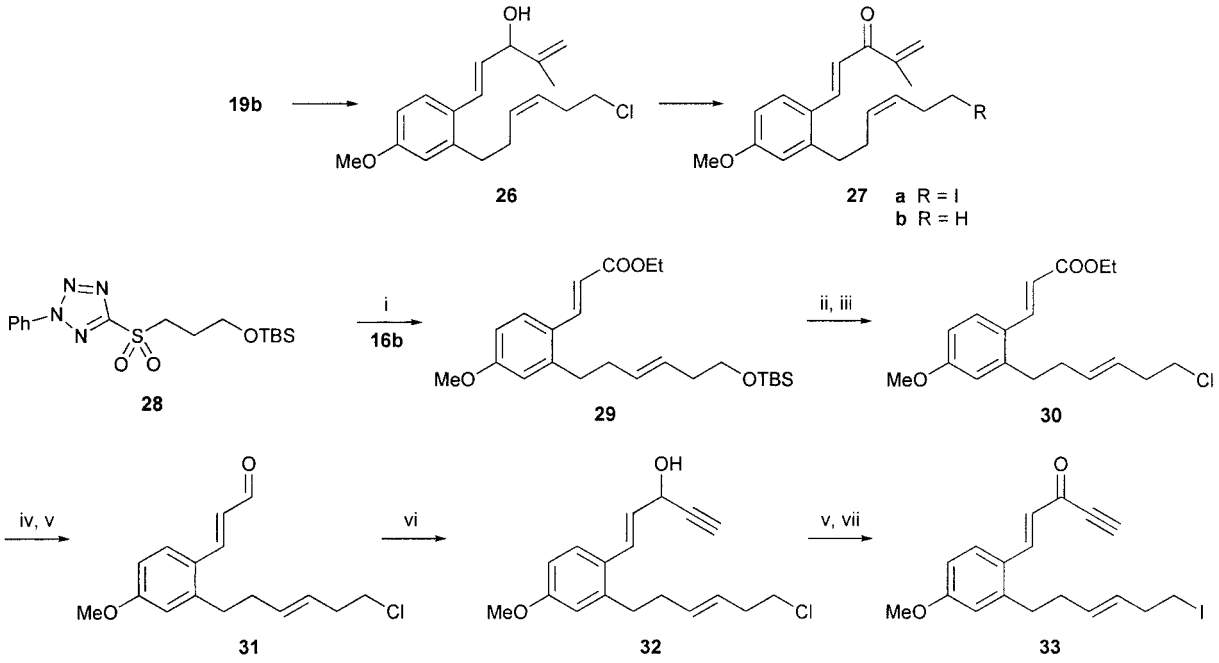
With the objective of incorporating unsaturation in the five-membered D ring, we next examined the cascade radical cyclization of the corresponding terminal acetylene analogue of **8b**, i.e., **23**, in the presence of Bu_3SnH/AIBN. Two crystalline tetracyclic products were produced in this cyclization in a combined yield of 63%. The structure and stereochemistry of the major product (≈40%) was established as the *trans*, *syn* diastereoisomer of the cyclopentaphenanthren-12-one (i.e., **24**) by single-crystal x-ray analysis, and the minor product was shown to be the *trans*, *syn*, *cis* diastereoisomer **25** of the 12-ketosteroid, **21b**. The structure and stereochemistry of the estrane **25**, which results from reduction of the enone **24** under the Bu_3SnH/AIBN reducing conditions followed from 1D NMR, correlated spectroscopy (COSY), heteronuclear multiple quantum correlation (HMQC), and nuclear Overhauser effect (NOE) difference experiments. Indeed, under better-controlled conditions, i.e., use of only 1.2 eq of Bu_3SnH, it was possible to isolate only the steroidal enone **24** in ≈50% yield from the reaction.

In addition to lacking methyl and carbonyl group substitution at C-18 and C-17,[†] respectively, neither of the synthesized tetracycles **21b** and **24** had the required *trans, anti, trans* B/C/D ring fused geometry for ultimate elaboration to estrone **1**. Therefore, we attempted to overcome some of these issues by studying the outcomes of the cascade radical cyclizations of the methyl-substituted iodotriene **27a** and the *E*- geometrical isomer **33** corresponding to the dienynone **23**.

The methyl-substituted iodotrienone **27a** was prepared from the corresponding substituted cinnamaldehyde **19b** by using the same sequence of reactions that had been used earlier to elaborate **8b** from **19b** (Scheme 4). Likewise, the *E*-alkene **33** was prepared in a straightforward manner and used an *E*-selective Julia olefination reaction between the aldehyde **16b** and the sulfone **28**, leading to the alkene **29**, which was then converted into **33** by using a sequence of reactions identical to those used to prepare **23** from **17**.

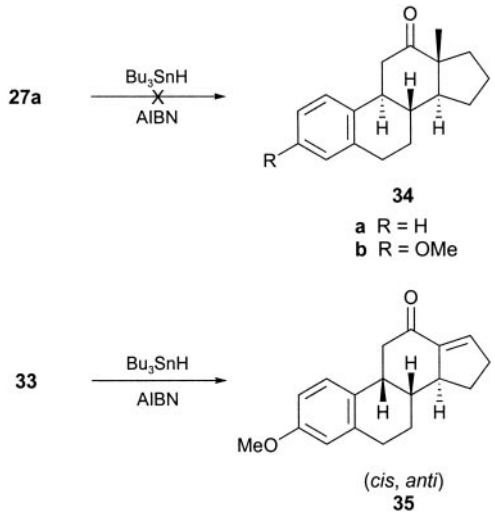
To our surprise, when the iododienone **27a** was treated with Bu_3SnH/AIBN, instead of the corresponding estrane (i.e., **34b**) the only product produced was that resulting from H-quench of the precursor radical, i.e., **27b**, in 62% yield. Whether this outcome was due to the additional steric bulk of the methyl group substituent on the enone electrophore in **27a** or occurred by an intramolecular H-quench from the same methyl group, producing a stabilized allylic radical, or both, is not known. However, when the *E*-iododienynone **33** was treated with Bu_3SnH/AIBN, it underwent the anticipated sequence of radical cyclizations and produced the estrane **35**, albeit in a disappointing 13% overall yield. No other products

[†]Steroid ring numbering is used throughout this paper.



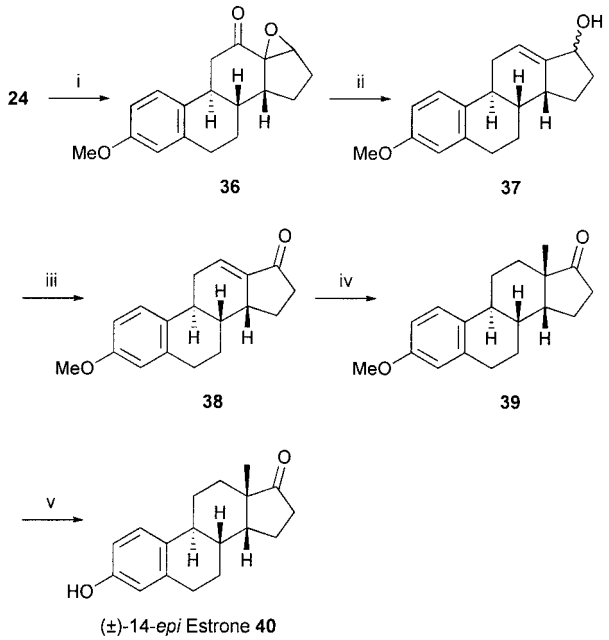
Scheme 4. (*i*) $TBSO(CH_2)_3SO_2$-2Ph-2*H*-tetrazole **28**, potassium hexamethyldisilazane, 77% yield; (*ii*) tetrabutylammonium fluoride, THF, 84% yield; (*iii*) *N*-chlorosuccinimide, PPh_3, Cl_2CH_2, 95% yield; (*iv*) iBu_2AlH, Cl_2CH_2, 80% yield; (*v*) MnO_2, Cl_2CH_2, 86–79% yield; (*vi*) HC≡CMgBr, THF, 62% yield; and (*vii*) NaI, MeCOEt, 82% yield.

resulting from this reaction could be characterized. The *cis*, *anti* stereochemistry of the 12-ketosteroid **35** followed from single-crystal x-ray analysis. In summary, the polyenynone **23** with *Z*-geometry in the iodohexenyl side chain undergoes a cascade of radical cyclizations leading to the *trans, syn* estrane **24**, whereas the corresponding *E*-isomer **33** undergoes the same series of cyclizations producing the diastereoisomeric *cis, anti* estrane **35**.



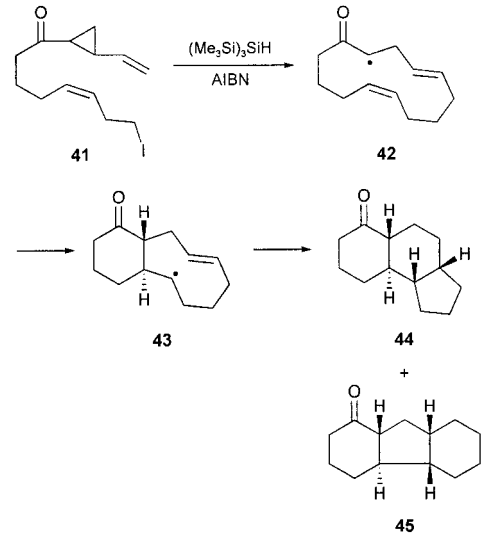
Because of the difficulty that we anticipated in attempting to epimerize selectively either the C-9 center in **35** or the C-14 center in **24** or any of the intermediates between them and *trans*, *anti*, *trans* estrone itself, we decided at this point to establish chemistry to convert the *anti, syn* tetracyclic enone **24** into 14-epiestrone **40**. After exploring a number of approaches (52), we carried out an enone transposition on **24**, using the Wharton procedure (53–55) which, in three steps, i.e., epoxidation (to **36**), hydrazone formation and fragmentation (to **37**), and oxidation, first gave the corresponding C12,C13 enone **38**. Reductive methylation of **38**, after conjugate addition of iBu_2AlH in THF/hexamethylphosphoramide (HMPA) at −50°C with methylcopper catalysis, and trapping the intermediate "ate" complex with MeI (56), was diastereoselective and next gave 14-epiestrone methyl ether **39** (Scheme 5). Finally, demethylation of **39** by using BBr_3 in THF gave 14-epiestrone **40**, as colorless crystals, identical to that described in the literature (57, 58).

After the success in elaborating the estra-1,3,5(10)-triene ring system, based on the cascade of radical cyclizations **8** → **9** (Scheme 1), we examined the alternative radical cascade **10** → **11** → **12** → **13** to estranes by using a vinylcyclopropane electrophore in the first radical macrocyclization step (Scheme 2). In an earlier investigation (59), we showed that the iodovinylcyclopropyl ketone **41** underwent a macrocyclization (to **42**) followed by successive transannulation reactions via **43** in the presence of $(Me_3Si)_3SiH$/AIBN, leading to a 1:2 mixture of the isomeric tricycles **44** and **45** in a combined yield of 65%. Therefore, we were optimistic that the analogous benzene-substituted vinylcyclopropane system **49** would take part in a similar sequence of cascade cyclizations leading to the corresponding estrane **50** (59). The iodovinylcyclopropanes **49a** and **49b** were synthesized in a straightforward manner from the earlier prepared cinnamates **17a** and **17b**, respectively, as outlined in Scheme 6. To our satisfaction, when the methoxy derivative **49b** was treated with Bu_3SnH/AIBN in refluxing benzene, work-up and chromatography separated the known *trans*, *anti*, *trans* diastereoisomer of the estrane **50b**, whose ^{13}C NMR spectroscopic data were identical with those reported in the literature (60). The estrane **50b** was produced alongside an unidentified tetracycle and also the product of reduction of the carbon-to-iodide bond in the starting material, in a combined yield of 45%. When the iodovinylcyclopropane **49a** was treated similarly with Bu_3SnH/AIBN, it too underwent a cascade of

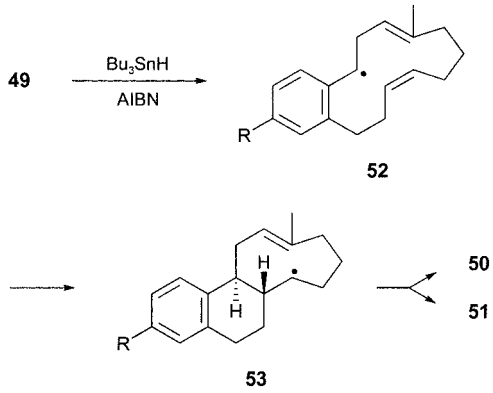


Scheme 5. (*i*) H_2O_2, NaOH, THF, *t*-BuOH, 40% yield; (*ii*) $NH_2NH_2{\cdot}H_2O$, HOAc, 30% yield; (*iii*) tetrapropylammonium perruthenate (TPAP), 4-methylmorpholine *N*-oxide (NMMO), 54% yield; (*iv*) hexamethylphosphoramide (HMPA), *i*-BuAlH, CuIMeLi; then MeI, 66% yield; and (*v*) BBr_3, THF, 79% yeild.

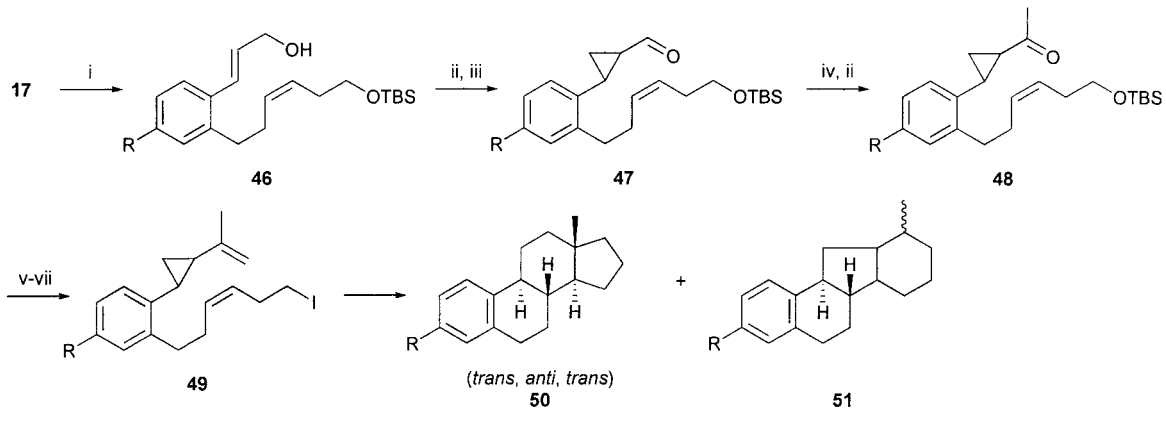
cyclizations but, instead of producing the corresponding estrane **50a**, it gave, in 25% yield, an isomeric compound whose spectroscopic data were comparable with those of the unidentified tetracyclic product produced alongside **50b** from **49b**. The new tetracycle produced from **49a** showed six methylene, five methine, and one methyl carbon signal in its ^{13}C NMR spectrum, which, with other data, supported assignment of the alternative 6,6,5,6-tetracyclic structure **51a** for this compound. However, we were not able to assign a relative stereochemistry for this interesting structure. Reflecting on the outcome of the triple radical cyclization from the related system **41**, leading to both **44** and **45**, it is perhaps not surprising that the corresponding radical cascade from the benzene-substituted vinylcyclopropane **49** would similarly produce mixtures of the tetracyclic products **50** and **51**. The radical cascade from **49** proceeds via **52** and then the 9-membered radical intermediate **53** (compare **43**), which, by



competing 5-*exo*/6-*endo*-trig transannulations could lead to either the 6,6,6,5- or the 6,6,5,6-tetracycle, i.e., **50** and **51**, as observed.



With the aforementioned model studies complete, but mindful of some limitations, we decided to synthesize the iodovinyl ether cyclopropane **55** and study its cascade radical cyclization to the



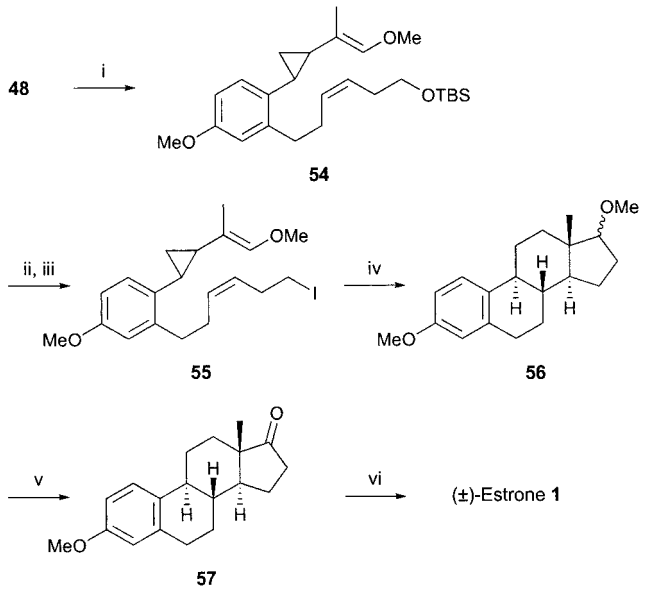
Scheme 6. (*i*) iBu_2AlH, Cl_2CH_2, 82% yield; (*ii*) Et_2Zn, CH_2I_2, 70% yield; (*iii*) pyridinium dichromate, 84% yield; (*iv*) $MePPh_3Br$, *n*-BuLi, 86% yield; (*v*) AcOH, THF, 95% yield; and (*vi*) I_2, imidazole, PPh_3, 73% yield.

estrane **56** en route to estrone **1**. Although imposing additional steric congestion at the vinylcyclopropane electrophore, the presence of the terminal vinyl methyl ether group in **55** was also expected to make this center more electrophilic to the incoming nucleophilic radical in the initial macrocyclization step in the overall radical cascade sequence.

The precursor iodovinyl ether cyclopropane **55** was synthesized from the previously prepared vinyl methyl ketone **48** by using a Horner–Wittig reaction with methoxymethyldiphenylphosphine oxide in the presence of lithium diisopropylamide, which first gave a 1:1 mixture of *Z* and *E* isomers of the intermediate **54**. Deprotection of **54** followed by treatment of the resulting alcohol with I_2, imidazole, and PPh_3, using procedures developed earlier in our studies, then gave the iodovinylcyclopropane **55** (Scheme 7).

To our satisfaction, when a solution of the iodide **55** in toluene at reflux was treated with Bu_3SnH/AIBN, work-up and chromatography gave the known 3,7-dimethoxyestrane **56** (61) as a crystalline solid, in 12–15% overall yield. The major product isolated, in 52% yield, was that corresponding to reduction of the carbon-to-iodide bond in the starting material. Bearing this in mind, and with a cascade of four C—C bond-forming reactions involved in the conversion **55** → **56**, each of the radical reactions proceeds with an average yield of ≈65%. Oxidation of the ring D methyl ether in **56** by using Jones' procedure next gave estrone methyl ether **57** which was then demethylated by using BBr_3, leading to (±)-estrone **1**, which had physical and spectroscopic properties identical with those described in the literature (62, 63).

In summary, two conceptually different radical-mediated cascade reactions from *ortho*-disubstituted aryl polyene and arylvinylcycloprane precursors, leading to the tricyclic B, C, and D rings of estranes in a single step, have been developed. The investigations culminated in a total synthesis of (±)-estrone **1**, and, separately, of 14-epiestrone **40**. Unfortunately, not all of the stereochemistries of the estranes prepared in model studies could be established unambiguously, and rationalization of the mechanisms of key events taking place during these cascade processes will remain a topic of conjecture until some of these issues are resolved. Nevertheless, a novel concept in the elaboration of ring A aromatic steroids from simple starting materials, in a single step, has been established, which could have wider applications in the synthesis of other polycyclic natural (and nonnatural) products.



Scheme 7. (*i*) $MeOCH_2POPh_2$, lithium diisopropylamide, THF, then NaH, THF, 90% yield; (*ii*) tetrabutylammonium fluoride, THF, 98% yield; (*iii*) I_2, imidazole, PPh_3, 80% yield; (*iv*) Bu_3SnH, AIBN, toluene, 12% yield; (*v*) CrO_3, catalytic H_2SO_4, Me_2CO, 94% yield; and (*vi*) BBr_3, THF, 79% yield.

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1. Anner, G. & Miescher, K. (1948) *Helv. Chim. Acta* **31,** 2173–2183.
2. Grieco, P. A., Takigawa, T. & Schillinger, W. J. (1980) *J. Org. Chem.* **45,** 2247–2251.
3. Funk, R. L. & Vollhardt, K. P. C. (1980) *J. Am. Chem. Soc.* **102,** 5253–5261.
4. Nicolaou, K. C., Barnette, W. E. & Ma, P. (1980) *J. Org. Chem.* **45,** 1463–1470.
5. Michellys, P.-Y., Pellissier, H. & Santelli, M. (1993) *Tetrahedron Lett.* **34,** 1931–1934.
6. Couturier, M. & Deslongchamps, P. (1996) *Synlett,* 1140–1142.
7. Ouellet, L., Langlois, P. & Deslongchamps, P. (1997) *Synlett,* 689–690.
8. Sakamoto, Y., Yasuharu, H. & Takahashi, T. (1995) *Synlett,* 231–232.
9. Pellissier, H. & Santelli, M. (1996) *Tetrahedron* **52,** 9093–9100.
10. Lavoie, R., Toró, A. & Deslongchamps, P. (1999) *Tetrahedron* **55,** 13037–13050.
11. Quinkert, G., Del Grosso, M., Döring, A., Döring, W., Schenkel, R. I., Bauch, M., Dambacher, G. T., Bats, J. W., Zimmermann, G. & Dürner, G. (1995) *Helv. Chim. Acta* **78,** 1345–1391.
12. Sugahara, T. & Ogasawara, K. (1996) *Tetrahedron Lett.* **37,** 7403–7406.
13. Vollhardt, K. P. C. (1985) *Pure Appl. Chem.* **57,** 1819–1826.
14. Lecker, S. H., Nguyen, N. H. & Vollhardt, K. P. C. (1986) *J. Am. Chem. Soc.* **108,** 856–858.
15. Sugihara, T., Coperet, C., Owczarczyk, Z., Harding, L. S. & Negishi, E. (1994) *J. Am. Chem. Soc.* **116,** 7923–7924.
16. Trost, B. M. & Shi, Y. (1993) *J. Am. Chem. Soc.* **115,** 9421–9438.
17. Corey, E. J. & Lin, S. (1996) *J. Am. Chem. Soc.* **118,** 8765–8766.
18. Fish, P. V., Johnson, W. S., Jones, G. S., Tham, F. S. & Kullnig, R. K. (1994) *J. Org. Chem.* **59,** 6150–6152.
19. Johnson, W. S., Wiedhaup, K., Brady, S. F. & Olson, G. L. (1974) *J. Am. Chem. Soc.* **96,** 3979–3984.
20. van Tamelen, E. E & Anderson, R. J. (1972) *J. Am. Chem. Soc.* **94,** 8225–8228.
21. van Tamelen, E. E., Holton, R. A., Hopla, R. E. & Konz, W. E. (1972) *J. Am. Chem. Soc.* **94,** 8228–8229.
22. Boehm, H. M., Handa, S., Pattenden, G., Roberts, L., Blake, A. J. & Li, W. S. (2000) *J. Chem. Soc. Perkin Trans. 1*, 3522–3538.
23. Double, P. & Pattenden G. (1998) *J. Chem. Soc. Perkin Trans. 1*, 2005–2008.
24. Pattenden, G., Roberts, L. & Blake, A. J. (1998) *J. Chem. Soc. Perkin Trans. 1,* 863–868.
25. Handa, S. Nair, P. S. & Pattenden, G. (2000) *Helv. Chim. Acta* **83,** 2629–2643.
26. Handa, S. & Pattenden, G. (1997) *Contemp. Org. Synth.* **4,** 196–215.
27. Curran, D. P. & Rakiewicz, D. M. (1985) *Tetrahedron* **41,** 3943–3958.
28. Caspar, M. L., Davis, D. G., Weng, X. & Zoretic, P. A. (1991) *Tetrahedron Lett.* **32,** 4819–4822.
29. Katouda, W., Sakamoto, Y., Takahashi, T., Tomida, S. & Yamada, H. (1995) *Tetrahedron Lett.* **36,** 2273–2276.
30. Ribeiro, A. A., Shen, Z., Wang, M. & Zoretic, P. A. (1995) *Tetrahedron Lett.* **36,** 2925–2928.
31. Ribeiro, A. A., Zhang, Y. & Zoretic, P. A. (1995) *Tetrahedron Lett.* **36,** 2929–2932.
32. Curran, D. P. & Jahn, U. (1995) *Tetrahedron Lett.* **36,** 8921–8924.
33. Chen, Z., Ribeiro, A. A., Zhang, Y. & Zoretic, P. A. (1996) *Tetrahedron Lett.* **37,** 7909–7912.
34. Sakamoto, Y., Takahashi, T., Tomida, S. & Yamada, H. (1997) *J. Org. Chem.* **62,** 1912–1913.
35. Fang, H., Ribeiro, A. A. & Zoretic, P. A. (1998) *J. Org. Chem.* **63,** 7213–7217.
36. Doi, T., Takahashi, T. & Tomida, S. (1999) *Tetrahedron Lett.* **40,** 2363–2366.
37. Ihara, M., Katsumata, A., Kuroyanagi, J. & Takasu, K. (1999) *Tetrahedron Lett.* **40,** 6277–6280.
38. Wu, S., Journet, M. & Malacria, M. (1994) *Tetrahedron Lett.* **35,** 8601–8604.
39. Batsanov, A., Chen, L., Gill, G. B. & Pattenden, G. (1996) *J. Chem. Soc. Perkin Trans. 1,* 45–55.
40. Handa, S., Pattenden, G. & Li, W.-S. (1998) *J. Chem. Soc. Chem. Commun.,* 311–312.
41. Porter, N. A., Magnin, D. R. & Wright, B. T. (1986) *J. Am. Chem. Soc.* **108,** 2787–2788.
42. Cox, N. J. G., Mills, S. D. & Pattenden, G. (1992) *J. Chem. Soc. Perkin Trans. 1*, 1313–1321.
43. Hitchcock, S. A. & Pattenden, G. (1990) *Tetrahedron Lett.* **31,** 3641–3644.
44. Hitchcock, S. A. & Pattenden, G. (1992) *J. Chem. Soc. Perkin Trans. 1*, 1323–1328.
45. Baldwin, J. E., Adlington, R. M. & Ramcharitar, S. (1992) *Tetrahedron* **48,** 3413–3428.
46. Porter, N. A., Chang, V. H.-T., Magnin, D. R. & Wright, B. T. (1988) *J. Am. Chem. Soc.* **110,** 3554–3560.
47. Myers, A. G. & Condroski, K. R. (1993) *J. Am. Chem. Soc.* **115,** 7926–7927.
48. Houldsworth, S. J., Pattenden, G., Pryde, D. C. & Thomson, N. M. (1997) *J. Chem. Soc. Perkin Trans. 1,* 1091–1093.
49. Pattenden, G., González, M. A., Little, P. B., Millan, D. S., Plowright, A. T., Tornos, J. A. & Ye, T. (2003) *Org. Biomol. Chem.* **1,** 4173–4208.
50. Jeffery, T. (1984) *J. Chem. Soc. Chem. Commun.,* 1287–1289.
51. Pattenden, G., McCulloch, S. & Cardente, M. A. G. (2001) *C. R. Acad. Sci. Ser. II*, 571–574.
52. Affo, W. (2003) Ph.D. thesis (Univ. of Nottingham, Nottingham, U.K.).
53. Wharton, P. S. (1961) *J. Org. Chem.* **26,** 4781–4782.
54. Barton, D. H. R., Motherwell, R. S. H. & Motherwell, W. B. (1981) *J. Chem. Soc. Perkin Trans. 1*, 2363–2367.
55. Filippo, M., Fezza, F., Izzo, I., De Riccardis, F. & Sodano, G. (2000) *Eur. J. Org. Chem.,* 3247–3252.
56. Satomi, H., Hayashi, T., Tsuda, T. & Saegusa, T. (1987) *J. Org. Chem.* **52,** 439–443.
57. Johns, W. F. & Johnson, W. S. (1957) *J. Am. Chem. Soc.* **79,** 2005–2009.
58. Prousa, R., Schonecker, B., Tresselt, D. & Ponsold, K. (1986) *J. Prakt. Chem.* **328,** 55–70.
59. Pattenden, G. & Wiedenau, P. (1997) *Tetrahedron Lett.* **38,** 3647–3650.
60. Zeigan, D., Radeglia, R. & Engelhardt, G. (1983) *J. Prakt. Chem.* **325,** 651–656.
61. Node, M., Hori, H. & Fujita, E. (1976) *J. Chem. Soc. Perkin Trans. 1,* 2237–2240.
62. Johnson, W. S., Christiansen, R. G. & Ireland, R. E. (1957) *J. Am. Chem. Soc.* **79,** 1995–2005.
63. Ciuffreda, P., Ferraboschi, P., Verza, E. & Manzocchi, A. (2001) *Magn. Reson. Chem.* **39,** 648–650.