COMMUNICATION

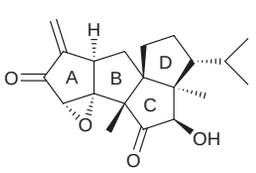
Carbonylative radical cyclization approaches to tri- and tetraquinanes: sequential formation of three, four and five carbon-carbon bonds

Dennis P. Curran,*[,a] Joseph Sisko,[a] Aaron Balog,[a] Noboru Sonoda,[b] Kiyoto Nagahara[b] and Ilhyong Ryu*[,b]

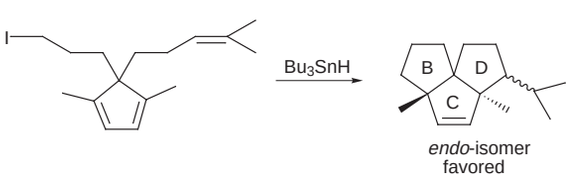
[a] *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, 15260, USA*
[b] *Department of Applied Chemistry, Osaka University, Suita, Osaka 565, Japan*

Tandem radical cyclizations and carbonylative tandem cyclizations of 5,5-disubstituted cyclopentadienes provide a variety of interesting products. Standard tandem cyclization of 9 provides an epimeric mixture of angular triquinanes, but carbonylative cyclization of the related precursors 7, 18 and 22 provides new products resulting from a 'round trip' radical rearrangement that occurs by a carbonylation, three successive cyclizations and a fragmentation. Double carbonylation of 25 occurs with triple cyclization and no fragmentation to produce tetracycle 26 as the principal product.

The interesting tetraquinane structure and biological activity of the natural product crinipellin A **1** and its congeners provide strong incentive to develop synthetic approaches to this class of molecules.[1] In 1993, Piers and Renaud reported the total synthesis of crinipellin B, and this remains the only total synthesis of a natural product in this family.[2] The tetraquinane structure of the crinipellins presents virtually limitless possibilities for designing approaches based on sequential radical reactions,[3,4] and we have previously reported model studies relevant to two very different approaches to the crinipellin ring system.[5] The model reaction shown in Scheme 1 is directed at the 'angular



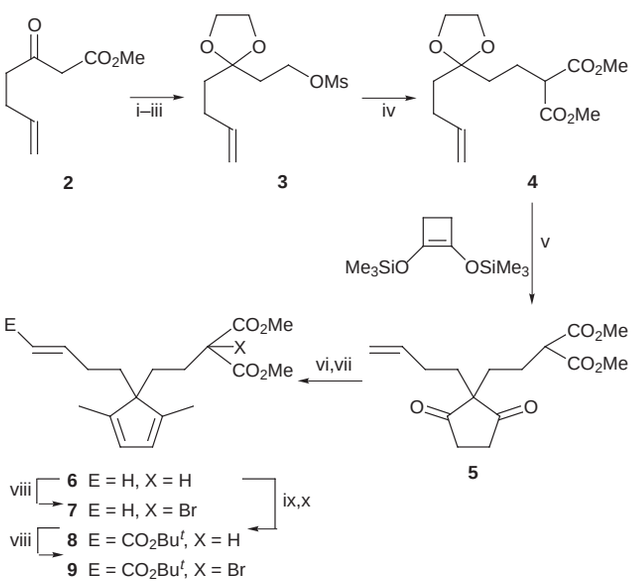
1 crinipellin A



Scheme 1

triquinane' portion of crinipellin (rings B–D), and was the first example of a tandem radical cyclization that formed non-vicinal C–C bonds.[5a] The joint interest of our research groups in the formation of geminal C–C bonds[6] has led to a number of interesting collaborative experiments that are the subject of this communication. We report herein carbonylative cyclizations of cyclopentadienes that form three, four and five new carbon-carbon bonds in a single process.

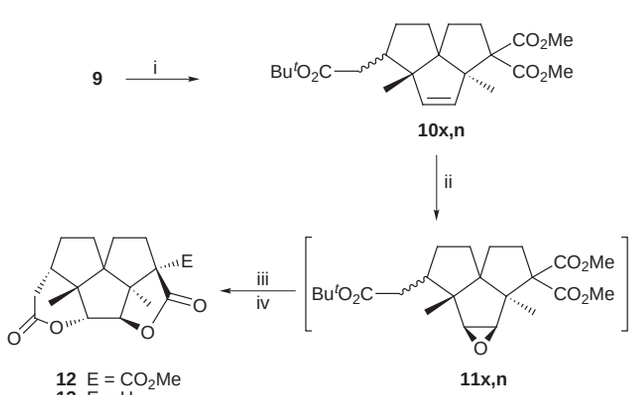
Precursor **6** was prepared on multigram scale by the route outlined in Scheme 2. Readily available acetoacetate derivative **2** was ketalized, reduced and mesylated. Alkylation of the methanesulfonate **3** with dimethyl malonate provided ketal **4**, which was then subjected to optimized conditions for a



Scheme 2 *Reagents and conditions*: i, ethylene glycol, *p*-TSA; ii, $LiAlH_4$; iii, MsCl, pyridine; iv, NaH, $CH_2(CO_2Me)_2$, DME, 80 °C; v, 15 equiv. $BF_3{\cdot}Et_2O$, CH_2Cl_2; vi, Ph_3PCH_3Br, BuLi; vii, HI, CH_3CN; viii, NaH, NBS; ix, OsO_4, NMO, then $NaIO_4$; $NaO^tC_5H_{11}$; x, NaH, $(EtO)_2P(O)CH_2CO_2Bu^t$

ring enlarging reaction with bis-trimethylsilyloxycyclobutene.[7,8] Bis-olefination of the resulting cyclopentanedione **5** and careful migration of the two double bonds into the ring with HI provided **6**, which was readily brominated to give **7**. Oxidative cleavage of **6** and olefination provided **8**, which was brominated to give **9**. Other precursors were either synthesized by an analogous route, or were made directly from **6**.[9]

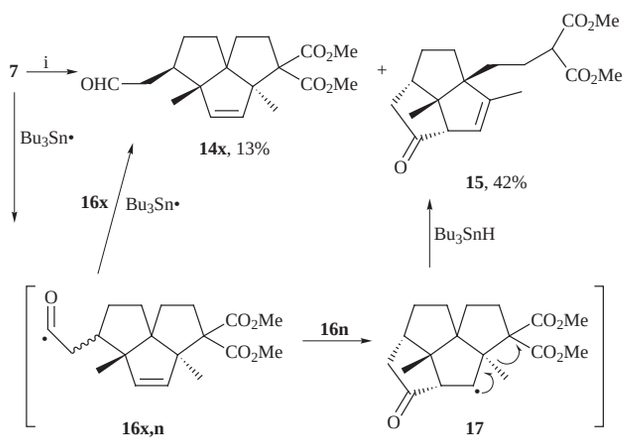
Double cyclization of bromide **9** provided a 2:1 mixture of tricycles **10x**,**n** in 89% yield (Scheme 3). That the *endo* product was major was shown by epoxidation. This provided an



Scheme 3 *Reagents and conditions*: i, 10% Bu_3SnH, $NaCNBH_3$, AIBN; ii, MCPBA; iii, stand at RT; iv, NaCl, H_2O, DMSO, 180 °C

unstable 2:1 mixture of epoxides **11**, probably *via* directed epoxidation involving one of the malonate esters. During the course of the epoxidation (several hours at room temperature), the major *endo*-isomer **11n** converted to bis-lactone **12**. Standard decarboxylation provided the nearly C_2-symmetric bis-lactone **13**, whose structure was proved by X-ray crystallography.[9] The bis-lactone **13** has two C-ring oxygens in place, and initially looked to be an attractive synthetic intermediate for the crinipellins. However, it subsequently proved to be very stable, and we did not discover any productive lactone opening reactions.

In principle, a carbonylative cyclization of **7** could provide a compound similar to **10** but in fewer steps. Therefore, we subjected **7** to standard carbonylative conditions (Scheme 4,

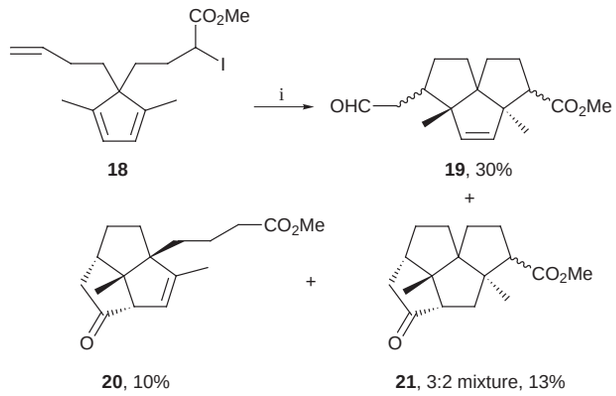


Scheme 4 *Reagents and conditions*: i, Bu_3SnH, CO, 85 atm, AIBN

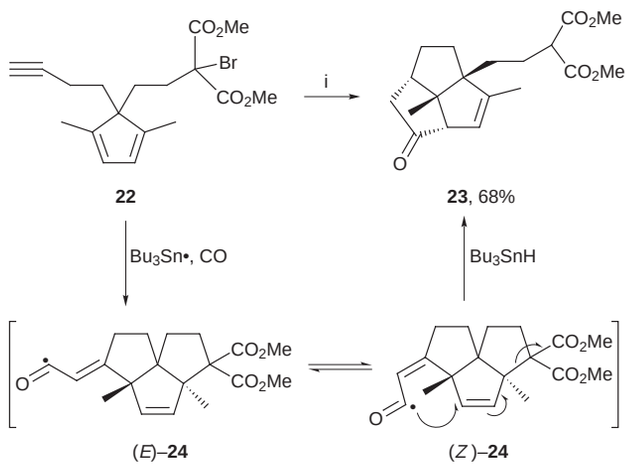
Bu_3SnH, AIBN, 85 atm CO).[10] This experiment produced two products: the expected *exo*-carbonylated product **14x** in 13% isolated yield and the unexpected tricycle **15** in 42% yield. The suggested mechanism for the formation of these two products is shown in Scheme 4. Double cyclization produces a mixture of *endo* (major) and *exo* (minor) radicals (not shown),[11] both of which are then carbonylated to afford **16**. The *exo*-product **16x** is then reduced to **14x** while the *endo*-product **16n** cyclizes back to the double bond to give **17**. The ensuing β-fragmentation of the carbon-carbon bond to the malonyl group is unusual but has precedent;[12] it is presumably driven to some extent by relief of ring strain. The conversion of **7** to **15** is a new approach to forming pentalenes from cyclopentadienes that entails the formation of three new C–C bonds with concomitant cleavage of one. It is also a new type of 'round trip' radical rearrangement[13] (the final radical ends up at the same location as the initial radical).

In the context of a crinipellin synthesis, the third cyclization is not necessarily disadvantageous since the ring might be cleaved by a Baeyer–Villiger oxidation which would install the required C-ring oxygen. We therefore investigated cyclization of the mono-ester **18** in an attempt to prevent the last fragmentation (Scheme 5). Carbonylative cyclization of **18** provided about 30% of a mixture of aldehydes **19** (4 isomers) along with 10% of the round trip product **20**[12c] and 13% of a 3:2 mixture of the tetracycles **21**. As expected from prior results,[5a] there is little stereoselectivity in the first cyclization.

Carbonylative cyclization of the alkyne analog **22** provided exclusively the round trip radical rearrangement product **23** in 68% yield (Scheme 6). In this reaction, we suspect that the initial carbonylation of the vinyl radical produces mainly the (*E*)-unsaturated acyl radical (*E*)-**24**, but this is known from recent work of Pattenden to readily equilibrate with the (*Z*)-isomer thanks to its α-ketenyl resonance form.[14] Back cyclization of (*Z*)-**24** and cleavage then provides the product **23**. We made one attempt to recyclize the fragmented bond by treat-



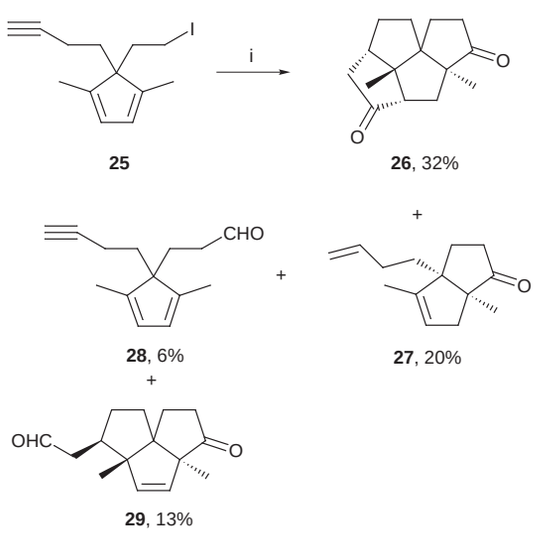
Scheme 5 *Reagents and conditions*: i, Bu_3SnH, CO, 80 atm, AIBN



Scheme 6 *Reagents and conditions*: i, Bu_3SnH, CO, 90 atm, AIBN

ment of **23** with manganese acetate,[15] but this gave a complex mixture.

Finally, we hypothesized that an additional carbonylation step could be inserted prior to the beginning of the cyclopentadiene cyclizations, and this hypothesis was tested by preparing iodide **25**. Carbonylation of **25** (Scheme 7) produced a



Scheme 7 *Reagents and conditions*: i, Bu_3SnH, CO, 95 atm, AIBN

mixture of five products, the most interesting of which was the tetracycle **26**. This results from a series of five sequential bond forming reactions (carbonylation, cyclization, cyclization, carbonylation, cyclization), four of which are non-vicinal. The second major product was **27**, which results from carbonylation

and 5-*exo* cyclization, but the subsequent allyl radical cyclization failed. Cyclization of a closely related acyl radical under non-carbonylative conditions also produced this side-product.[5a] The minor product **28** missed a cyclization, while aldehyde **29** is the expected product when the second cyclization occurs in an *exo*-fashion.

These results underline the power of combining tandem radical cyclizations with carbonylations. A diverse array of complex tri- and tetra-quinanes can be generated from simple and readily available 5,5-disubstituted cyclopentadienes with moderate to excellent levels of control. The results will be of value in planning future work in the crinipellin area as well as in other areas of polyquinane synthesis.

Acknowledgements

D. P. C. thanks the National Institutes of Health (NIH) for funding, and J. S. thanks the NIH for a postdoctoral fellowship. A. B. thanks the American Chemical Society for a Division of Organic Chemistry Fellowship. I. R. thanks the Sumitomo Foundation and the Ministry of Education, Science and Culture of Japan for financial support. We thank Prof. Mitsuo Komatsu for helpful discussions.

References

1 (*a*) T. Anke, J. Heim, F. Knoch, U. Mocek, B. Steffan and W. Steglich, *Angew. Chem.*, *Int. Ed. Engl.*, 1985, **97**, 709; (*b*) J. Kupka, T. Anke, F. Oberwinkler, G. Schramm and W. Steglich, *J. Antibiot.*, 1979, **32**, 130.

2 (*a*) E. Piers and J. Renaud, *J. Org. Chem.*, 1993, **58**, 11. Other model studies: (*b*) G. Mehta, K. S. Rao and M. S. Reddy, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 693; (*c*) L. V. Tinao-Wooldridge, K. D. Moeller and C. M. Hudson, *J. Org. Chem.*, 1994, **59**, 2381; (*d*) D. A. Frey, J. A. Marx and K. D. Moeller, *Electrochim. Acta*, 1997, **42**, 1967; (*e*) A. L. Veretenov, W. A. Smit, L. G. Vorontsova, M. G. Kurella, R. Caple and A. S. Gybin, *Tetrahedron Lett.*, 1991, **32**, 2109.

3 (*a*) D. P. Curran, *Synlett*, 1991, 63; (*b*) D. P. Curran, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 4, p. 779.

4 Computer analysis of only the approaches with vicinal bond forming reactions reveals >100 possibilities. G. Mehta, R. Barone, P. Azario, F. Barberis, M. Arbelot and M. Chanon, *Tetrahedron*, 1992, **48**, 8953.

5 (*a*) C. E. Schwartz and D. P. Curran, *J. Am. Chem. Soc.*, 1990, **112**, 9272; (*b*) D. P. Curran, J. Sisko, P. E. Yeske and H. Liu, *Pure Appl. Chem.*, 1993, **65**, 1153; (*c*) D. P. Curran and S. Sun, *Aust. J. Chem.*, 1995, **48**, 261.

6 I. Ryu, N. Sonoda and D. P. Curran, *Chem. Rev.*, 1996, **96**, 177.

7 T. J. Jenkins and D. J. Burnell, *J. Org. Chem.*, 1994, **59**, 1485.

8 A. Balog, S. J. Geib and D. P. Curran, *J. Org. Chem.*, 1995, **60**, 345.

9 Full details of the synthesis and characterization of all precursors as well as the X-ray structure can be found in the PhD Thesis of A. Balog, University of Pittsburgh, 1996.

10 I. Ryu and N. Sonoda, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 1050.

11 For a review of stereoselection in radical cyclizations, see D. P. Curran, N. A. Porter and B. Giese, in *Stereochemistry of Radical Reactions: Concepts*, *Guidelines*, *and Synthetic Applications*, VCH, Weinheim, 1996, ch. 2, p. 283.

12 For example, see: (*a*) D. P. Curran, E. Eichenberger, M. Collis, M. G. Roepel and G. Thoma, *J. Am. Chem. Soc.*, 1994, **116**, 4279; (*b*) M. Newcomb, J. H. Horner and C. J. Emanuel, *J. Am. Chem. Soc.*, 1997, **119**, 7147; (*c*) I. Ryu, H. Muraoka, N. Kambe, M. Komatsu and N. Sonoda, *J. Org. Chem.*, 1996, **61**, 6396.

13 (*a*) B. P. Branchaud, A. G. Glenn and H. C. Stiasny, *J. Org. Chem.*, 1991, **56**, 6656; (*b*) B. P. Branchaud, M. P. Montague-Smith, D. J. Kosman and F. R. McLaren, *J. Am. Chem. Soc.*, 1993, **115**, 798.

14 (*a*) C. J. Hayes and G. Pattenden, *Tetrahedron Lett.*, 1996, **37**, 271; (*b*) See also, I. Ryu, T. Okuda, K. Nagahara, N. Kambe, M. Komatsu and N. Sonoda, *J. Org. Chem.*, 1997, **62**, 7550.

15 B. B. Snider, *Chem. Rev.*, 1996, **96**, 339.

Paper 8/00352A
Received 8*th January* 1998
Accepted 3*rd April* 1998