COMMUNICATION

A new cycloheptenone annulation method: use of the bifunctional reagent (*Z*)-5-iodo-1-tributylstannylpent-1-ene in organic synthesis

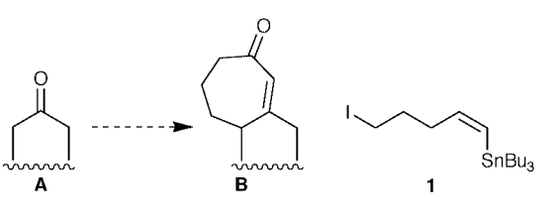
Edward Piers,* Shawn D. Walker and Ralph Armbrust

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia, Canada V6T 1Z1. Fax: 1-604-822-2847; E:mail: epier@interchange.ubc.ca

Received (in Cambridge, UK) 21st December 1999, Accepted 1st February 2000

A new seven-membered annulation method that employs (*Z*)-5-iodo-1-tributylstannylpent-1-ene (1) as a key reagent and that is exemplified by the conversion of compounds 6, 12, 13, 20, 25, and 26 into the annulation products 11, 18, 19, 24, 33, and 34, respectively, is reported.

Seven-membered carbocycles commonly make up part of the constitution of a variety of structurally novel, biologically interesting natural products. Over the years, a number of methods for the construction of seven-membered rings have been devised and successfully employed in complex molecule synthesis. Examples of such methods include the homo-Cope rearrangement of 1,2-divinylcyclopropane systems,[1] ring expansion reactions,[2] and cycloaddition processes [4 + 3 (see ref. 3) and 5 + 2 (see ref. 4)]. In connection with another study in progress in our laboratory, we wished to carry out a seven-membered ring annulation shown in general terms by the conversion of a ketone **A** into a cycloheptenone **B** (Scheme 1). We

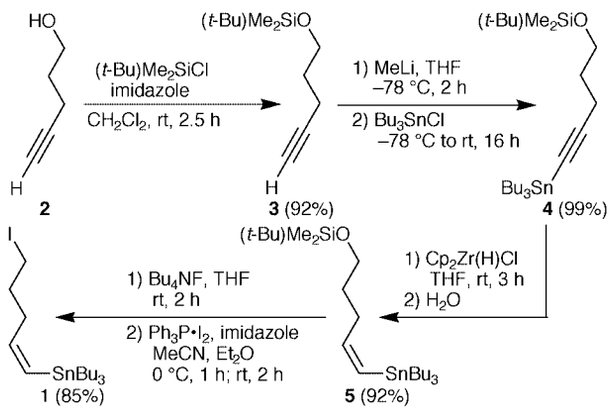


Scheme 1

report herein the development of a new, concise protocol for effecting such annulations. The novel bifunctional reagent (*Z*)-5-iodo-1-tributylstannylpent-1-ene (**1**) played a pivotal role in the elaboration of this new method.

The alkenylstannane **1** was prepared as shown in Scheme 2. Commercial pent-4-yn-1-ol (**2**) was converted into the silyl ether **3**,† which, upon deprotonation with MeLi and reaction of the resultant lithium acetylide with Bu_3SnCl, afforded the alkynylstannane **4**. Subjection of **4** to hydrozirconation with Schwartz's reagent,[5] followed by protonation of the resultant intermediate,[6] produced the required (*Z*)-alkenylstannane **5**. Routine fluoride-induced cleavage of the silyl ether of **5** and reaction of the acquired alcohol with $Ph_3P{\cdot}I_2$–imidazole[7] gave the key bifunctional reagent **1**. The overall yield of **1** from pent-4-yn-1-ol (**2**) was ~70%. Substance **1** was stored in the dark over copper wire and, under these conditions, has been found to be stable for over one year at ambient temperature.

The new annulation protocol is illustrated initially by the transformation of the dimethylhydrazone **6**[8] into the bicyclic cycloheptenone **11**, as summarised in Scheme 3. Treatment of **6** with LDA in THF at −78 °C and then at 0 °C, followed by addition of HMPT, cooling to −78 °C, addition of the electrophile **1**, and warming of the reaction mixture to rt, provided the alkylated[9] hydrazone **7**. In order to avoid the possibility of protiodestannylation of the alkenylstannane function during hydrolysis of the hydrazone moiety, the intermediate **7** was subjected to iododestannylation,[10] which provided, stereospecifically, the iodide **8**. At this stage, hydrolysis[11] of the hydrazone

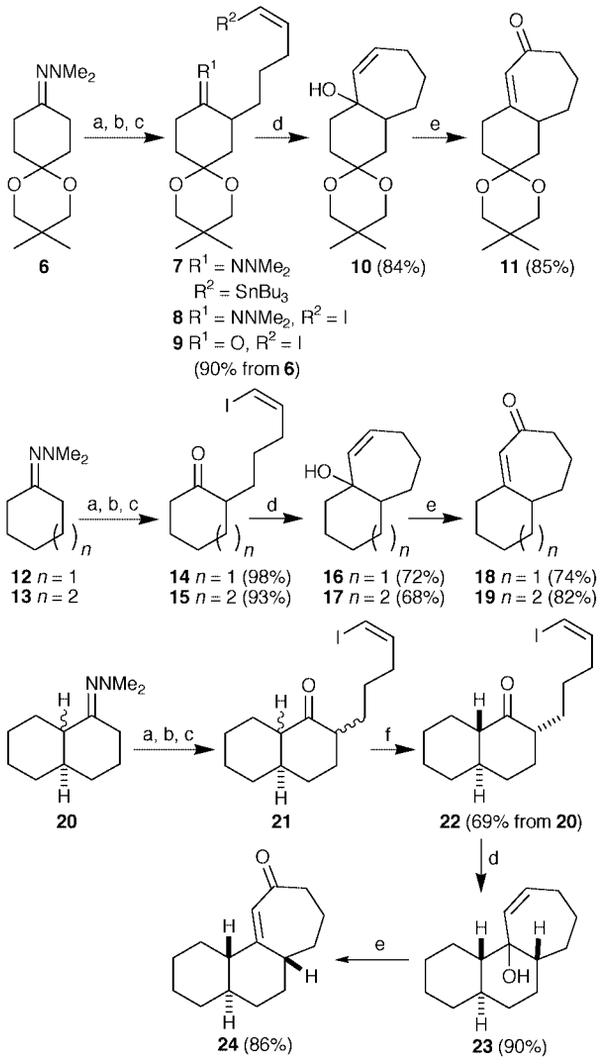


Scheme 2

unit by treatment of **8** with ethanoic acid–sodium ethanoate in aqueous THF at rt produced the ketone **9**. It should be noted that the three-step conversion of **6** into **9**, which was easily and conveniently performed without purification of the intermediates **7** and **8**, was highly efficient and produced **9** in an overall yield of 90%. Treatment of a cold (−78 °C) THF solution of **9** with BuLi (2.1 equiv.)[12] produced, after a suitable work-up procedure, the ring-closed product **10** in 84% yield as a single diastereomer of undetermined configuration. The annulation process (~64% overall yield, **6**→**11**) was completed by treatment of **10** with PCC[13] in the presence of 3 Å molecular sieves.[14] Typically, in this and subsequent oxidative conversions of tertiary allylic alcohols to the corresponding cycloheptenones, ~0.85 g of molecular sieves per mmol of substrate was employed. The sieves were powdered and flame-dried under reduced pressure (vacuum pump) prior to use. In general, the oxidative conversions in the presence of the molecular sieves were superior (*i.e.*, faster and more efficient) to those carried out in the absence of the sieves.

Subjection of the dimethylhydrazones **12**, **13**, and **20** to the alkylation–iododestannylation–hydrolysis protocol described above provided the iodo ketones **14**, **15**, and **21**, respectively, in overall yields >90%. The product **21**, which consisted of three diastereomers, was equilibrated with sodium methoxide in methanol. Purification of the resultant material by chromatography on silica gel afforded the most stable diastereomer **22** in 69% overall yield from **20**. Butyllithium-induced ring closure[12] of **14**, **15**, and **22** furnished the tertiary allylic alcohols (**16**, **17**, **23**, respectively) in good-to-excellent yields. Although **16** was produced as a mixture of epimers (~5:1), the alcohols **17** and **23** were obtained in diastereomerically pure form. The relative configurations at the newly formed ring junctions of these materials are of no consequence to the overall annulation processes and, consequently, were not determined. The only other product detected in each of these reactions was uncyclized material in which the iodine of the starting material was replaced by a hydrogen. In each case, this (minor) product was readily separated from the requisite alcohol by flash chromato-

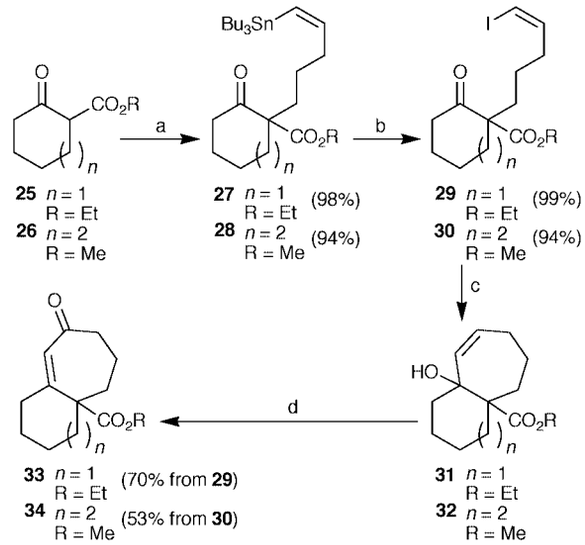
DOI: 10.1039/a909922k



Scheme 3 *Reagents and conditions*: (a) i, LDA, THF, −78 °C, 5 min, then 0 °C, 2 h; ii. **1**, THF–HMPT, −78 °C to rt, 15 h; (b) I_2, CH_2Cl_2, rt, 15 min; (c) HOAc, NaOAc, THF H_2O, rt, 15 min for **9**; 3 h for **14**, **15**, and **21**; (d) BuLi (2.1 equiv.), THF, −78 °C, 1 h; (e) PCC (2–3 equiv.), 3 Å molecular sieves, CH_2Cl_2, rt, 2 h for **10**; 23 h for **16**; 1 h for **17**; 3 h for **23**; (f) NaOMe, MeOH, rt, 15 h.

graphy of the mixture on silica gel. Exposure of each of the compounds **16**, **17**, and **23** to PCC[13] in the presence of 3 Å molecular sieves[14] provided the enone annulation products **18** (74%), **19** (82%), and **24** (86%), respectively. It should be noted that the oxidative conversion **16**→**18** was slower than the transformations **17**→**19** and **23**→**24**. Monitoring the oxidation of **16** by TLC indicated that one diastereomer of **16** was transformed into **18** at a rate slower than that of the other isomer. However, the reaction was complete after the mixture had been stirred overnight.

Application of the new method was extended to annulation of cyclic β-keto ester substrates (Scheme 4). Reaction of iodide **1** with the potassium enolates of the keto esters **25** and **26** in refluxing THF led to excellent yields of the alkylated products **27** and **28**. Treatment of each of these substances with I_2 in dichloromethane smoothly effected iododestannylation to produce the iodides **29** and **30**. Experimentation showed that, compared with the substrates (**9**, **14**, **15**, **22**) discussed above, the BuLi-mediated cyclisations of the iodides **29** and **30** are more efficiently carried out at 0 °C than at −78 °C. Thus, treatment of **29** and **30** with BuLi under the conditions given in Scheme 4 provided very good yields of the corresponding bicycles **31** and **32**. In each case, the desired alcohol (a single diastereomer, configuration undefined) was accompanied by minor amounts of uncyclised protiodeiodinated material. At −78 °C, the amount of these synthetically unproductive by-



Scheme 4 *Reagents and conditions*: (a) i, KH, THF, rt, 45 min; ii, **1**, THF, reflux, 15–17 h; (b) I_2, CH_2Cl_2 rt, 15 min; (c) BuLi (2.1 equiv.), THF, 0 °C, 45 min; (d) PCC (2–3 equiv.), 3 Å molecular sieves, CH_2Cl_2, reflux, 5.5 h for **31**; 2.5 h for **32**.

products increased. It should be noted that, with respect to the cyclisation process, the reactions were highly chemoselective. No products that would have resulted from ring closure involving the ester carbonyl functions could be detected in the crude product mixtures.

Since any uncyclised by-products produced in the reactions were difficult to separate chromatographically from the required tertiary allylic alcohols **31** and **32**, the crude products were subjected directly to oxidation with PCC[13] in refluxing dichloromethane containing 3 Å molecular sieves.[14] Subsequent purification of the crude products by chromatography on silica gel gave the enones **33** and **34** in moderate overall yields from **29** and **30**, respectively.

The dramatic beneficial effect of using molecular sieves in the PCC oxidation of **31** and **32** deserves emphasis. Oxidations of the (crude) allylic alcohols **31** and **32** under other conditions (*e.g.* PCC, NaOAc, CH_2Cl_2;[13] PCC adsorbed on alumina[15] in refluxing CH_2Cl_2 or refluxing benzene) were very slow and required long reaction times (~2 days) with a large excess of PCC in order to drive the reaction to completion. Unfortunately, these forcing conditions led to concomitant formation of polar by-products and gave low yields of the enones. These difficulties were largely circumvented when the protocol outlined above (Scheme 4) was employed.

In summary, the bifunctional reagent **1** has been successfully employed in the development of a new cycloheptenone annulation method. The individual reactions involved are experimentally straightforward and the overall yields of the annulation processes are good to excellent. Of particular note are the high yields associated with the BuLi-mediated ring closure of seven-membered rings in the transformations of **9**, **14**, **15**, **22**, **29**, and **30** into **10**, **16**, **17**, **23**, **31**, and **32**, respectively. Extensions of this method to natural product synthesis are being investigated and the results will be reported in due course.

Experimental

Preparation of the keto iodide 9

To a cold (−78 °C), stirred solution of LDA (5.82 mmol) in dry THF (15 ml) was added, *via* a cannula, a solution of the dimethylhydrazone **6** (1.40 g, 5.82 mmol) in dry THF (3.5 ml). The mixture was stirred for 5 min at −78 °C and then for 2 h at 0 °C. Dry HMPT (2.03 ml, 11.66 mmol) was added *via* a syringe and the mixture was stirred at 0 °C for 10 min and then was cooled to −78 °C. A solution of the bifunctional reagent **1** (1.41 g, 2.91 mmol) in dry THF (3 ml) was added dropwise *via* a

cannula. The mixture was stirred at −78 °C for 2 h and then was allowed to warm to rt overnight. The stirred mixture was treated sequentially with saturated aqueous $NaHCO_3$ (30 ml), Et_2O (60 ml) and H_2O (30 ml) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 ml) and the combined organic extracts were washed (brine, 4 × 40 ml), dried ($MgSO_4$), and concentrated. The residual material was dissolved in dry CH_2Cl_2 (30 ml). To the resultant vigorously stirred solution at rt was added dropwise, by syringe, 30 ml of a 0.1 M solution of I_2 in CH_2Cl_2 and stirring was continued for an additional 15 min. The solution was treated with saturated aqueous $Na_2S_2O_3$ (30 ml), the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed (5% aqueous $NaHCO_3$, 1 × 40 ml; brine, 2 × 60 ml), dried ($MgSO_4$), and concentrated. To the residual oil was added, sequentially, THF (3.8 ml), H_2O (0.85 ml), NaOAc (1.7 g), and HOAc (5.4 ml). The mixture was stirred at rt for 15 min and then was neutralized by addition of solid $NaHCO_3$. Et_2O (100 ml) and H_2O (350 ml) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 100 ml) and the combined organic extracts were washed (brine, 75 ml), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (100 g TLC-grade silica gel, 9 : 1 and then 4 : 1 petroleum ether–Et_2O) and the acquired oil was distilled (bulb-to-bulb, 220–230 °C/0.5 Torr) to afford 1.03 g (90%) of compound **9**, a pale yellow oil; ν_{max}/cm^{-1} (neat) 1713vs (CO), 1610 (C=C); δ_H ($CDCl_3$, 400 MHz) 0.96 (s, 3 H), 1.00 (s, 3 H), 1.17–1.86 (m, 6 H), 2.09–2.15 (m, 2 H), 2.24–2.31 (m, 1 H), 2.45–2.55 (m, 4 H), 3.52 (s, 2 H), 3.54 (s, 2 H), 6.12–6.18 (m, 2 H); δ_C ($CDCl_3$, 75.3 MHz) 22.5, 22.6, 25.2, 28.1, 30.1, 31.5, 34.6, 37.0, 38.1, 44.6, 70.3, 70.6, 82.6, 96.3, 140.8, 211.5 (Found: C, 48.9; H, 6.2. Calc. for $C_{16}H_{25}IO_3$: C, 49.0; H, 6.4%).

Preparation of the tertiary allylic alcohol 10

To a cold (−78 °C), stirred solution of compound **9** (475 mg, 1.21 mmol) in dry THF (70 ml) was added, in a single rapid injection with a syringe, a solution of BuLi (2.54 mmol, 2.1 equiv.) in hexanes. The reaction mixture was stirred at −78 °C for 1 h and then was treated with saturated aqueous $NaHCO_3$ (20 ml). The mixture was warmed to rt, H_2O (20 ml) and Et_2O (40 ml) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 ml) and the combined organic extracts were washed (brine, 1 × 30 ml), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (30 g of TLC-grade silica gel, 3 : 2 petroleum ether–Et_2O) to provide 271 mg (84%) of **10**, a colourless oil that solidified to give colourless crystals, mp 69–70 °C; ν_{max}/cm^{-1} (KBr) 3495s (OH) 1654 (C=C); δ_H ($CDCl_3$, 400 MHz) 0.89 (s, 3 H), 1.00 (s, 3 H), 1.24 (s, 1 H), 1.45–1.91 (m, 10 H), 2.09–2.23 (m, 3 H), 3.40 (dd, 1 H, *J* 11, 1 Hz), 3.46 (dd, 1 H, *J* 11, 1 Hz), 3.47 (d, 1 H, *J* 11 Hz), 3.56 (d, 1 H, *J* 11 Hz), 5.48 (d, 1 H, *J* 12 Hz), 5.78 (ddd, 1 H, *J* 12, 6, 6 Hz); δ_C ($CDCl_3$, 75.3 MHz) 22.6, 22.8, 25.8, 27.5, 27.6, 30.2, 32.8, 37.8, 37.9, 39.4, 70.0, 70.1, 72.0, 97.6, 133.4, 138.2 (Found: C, 72.0; H, 10.0. Calc. for $C_{16}H_{26}O_3$: C, 72.1; H, 9.8%).

Preparation of the bicyclic cycloheptenone 11

To a stirred solution of alcohol **10** (136 mg, 0.510 mmol) in dry CH_2Cl_2 (2 ml) was added consecutively dry, powdered 3 Å molecular sieves (434 mg) and PCC (220 mg, 2 equiv.) and the brown mixture was stirred at rt for 2 h. Et_2O (10 ml) was added and the mixture was stirred for 1 h at rt and then was filtered through a thin pad of Florisil®. The collected material was washed with Et_2O (~400 ml) and EtOAc (~100 ml) until no UV-active product was detected in the eluate. The combined eluate was concentrated and the crude product was purified by flash chromatography (13 g of TLC-grade silica gel, 3 : 2 petroleum ether–Et_2O) to provide 115 mg (85%) of the enone **11**, a colourless oil that solidified to afford colourless crystals, mp 94.5–95 °C; ν_{max}/cm^{-1} (KBr) 1636vs (CO); δ_H ($CDCl_3$, 400 MHz) 0.91 (s, 3 H), 1.00 (s, 3 H), 1.37–1.48 (m, 3 H), 1.63–1.73 (m, 1 H), 1.78–1.87 (m, 1 H), 1.91–1.98 (m, 1 H), 2.17–2.23 (m, 2 H), 2.37–2.46 (m, 2 H), 2.50–2.64 (m, 3 H), 3.46 (d, 2 H, *J* 11 Hz), 3.52 (d, 1 H, *J* 11 Hz), 3.54 (d, 1 H, *J* 11 Hz), 5.89 (s, 1 H); δ_C ($CDCl_3$, 75.3 MHz) 20.1, 22.5, 22.7, 30.2, 32.0, 33.4, 34.8, 40.7, 41.5, 44.3, 70.2, 70.3, 96.8, 126.8, 158.9, 204.3 (Found: C, 72.6; H, 9.4. Calc. for $C_{16}H_{24}O_3$: C, 72.7; H, 9.15%).

Acknowledgements

We thank the NSERC of Canada and the Merck Frosst Centre for Therapeutic Research for financial support. Postgraduate scholarships (to S. D. W.) from NSERC (Canada) and FCAR (Quebec) are also gratefully acknowledged.

Notes and references

† All isolated and purified compounds reported herein exhibit spectra in accord with the assigned structures and gave satisfactory elemental (C, H) analyses and/or molecular mass determinations (high resolution mass spectrometry).

1 T. Hudlicky, R. Fan, J. W. Reed and K. G. Gadamasetti, *Org. React.*, 1992, **41**, 1.
2 (*a*) P. M. Wovkulich, in *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 1, ed. S. L. Schreiber, p. 843; (*b*) S. Yang, B. Hungerhoff and P. Metz, *Tetrahedron Lett.*, 1998, **39**, 2097, and references therein.
3 (*a*) A. Hosomi and Y. Tominaga, in *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 5, ed. L. A. Paquette, p. 593; (*b*) M. Harmata, *Tetrahedron*, 1997, **53**, 6235.
4 (*a*) P. A. Wender, L. Siggel and J. M. Nuss, in *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 5, ed. L. A. Paquette, p. 645; (*b*) P. A. Wender, A. J. Dyckman, C. O. Husfeld, D. Kadereit, J. A. Love and H. Rieck, *J. Am. Chem. Soc.*, 1999, **121**, 10442, and references therein.
5 J. Schwartz and J. A. Labinger, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 333.
6 B. H. Lipshutz, R. Keil and J. C. Barton, *Tetrahedron Lett.*, 1992, **33**, 5861.
7 P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2866.
8 E. Piers and R. W. Friesen, *Can. J. Chem.*, 1992, **70**, 1204.
9 E. J. Corey and D. Enders, *Chem. Ber.*, 1978, **111**, 1337.
10 E. Piers and P. D. Coish, *Synthesis*, 1995, 47, and references therein.
11 E. J. Corey and H. L. Pearce, *J. Am. Chem. Soc.*, 1979, **101**, 5841.
12 E. Piers and P. C. Marais, *Tetrahedron Lett.*, 1994, **35**, 8573.
13 (*a*) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647; (*b*) G. Piancatelli, A. Scettri and M. D'Auria, *Synthesis*, 1982, 245.
14 J. Herscovici, M.-J. Egron and K. Antonaskis, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1967.
15 Y.-S. Cheng, W.-L. Liu and S. Chen, *Synthesis*, 1980, 223.

Communication a909922k