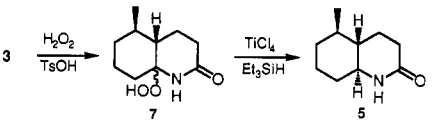
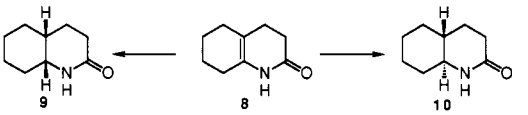
we have found that hydrogenation of ene–lactam **3** occured over 5% palladium on charcoal in EtOH/AcOH (5/1) in the presence of a catalytic amount of HCl at 60 °C under H_2 (80 atm) to give (4a*S*,5*R*,8a*R*)-5-methyl-2,3,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**4**) (mp 146.5–147.5 °C; $[\alpha]^{25}_D$ –60.4° (*c* 1.00, $CHCl_3$) highly selectively. The diastereomeric ratio of **4** (4a*S*,5*R*,8a*R*)/its isomer **5** (4a*S*,5*R*,8a*S*) was determined to be 98/2 by GLC analysis (capillary column, PEG-20M, 25 m). The lactam **4** thus obtained was converted into **1** ($[\alpha]^{21}_D$ –16.2° (*c* 1.00, CH_3OH))[13] by the reported method.[9b]

Selective formation of cis-fused lactam **4** can be rationalized by assuming diastereoselective protonation of **3** to give acyl iminium ion **6** which undergoes subsequent hydrogenation. Consequently, trapping of **6** with suitable nucleophiles and subsequent selective transformation would give trans-fused products. Indeed, treatment of **3** with H_2O_2 in the presence of TsOH catalyst gave unstable (4a*S*,5*R*)-8a-hydrodioxy-5-methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**7**) [77%, 4a*S*,5*R*,8a*R*/4a*S*,5*R*,8a*S* = 2/1], which was converted into (4a*S*,5*R*,8a*S*)-lactam **5** (mp 180–180.5 °C, $[\alpha]^{25}_D$ + 14.7° (*c* 1.06, $CHCl_3$)) upon treatment with Et_3SiH in CH_2Cl_2 in the presence of $TiCl_4$ [72% yield, **5**/**4** = 90/10]. We



are in a position to be able to prepare either cis- or trans-fused decahydroquinolines selectively by the acid-promoted catalytic hydrogenation of ene–lactams or the acid-promoted reaction of ene–lactams with H_2O_2 followed by treatment with Et_3SiH in the presence of $TiCl_4$. Simply, *cis*- and *trans*-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**9** and **10**) can be prepared selectively (**9**/**10** = 92/8, **9**/**10** = 7/93) from 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (**8**) by using our methods. The details of the mechanism and the extension of the useful catalytic reactions to the other systems are under active study.



Supplementary Material Available: Experimental procedures and spectral data for all compounds (11 pages). Ordering information is given on any current masthead page.

(13) The HCl salt of (–)-**1**, mp 286–288 °C (sealed capillary) (lit.[9c] mp 288–290 °C (sealed capillary)); $[\alpha]^{21}_D$ –16.2° (*c* 1.00, CH_3OH) (lit.[9c] $[\alpha]^{20}_D$ –14.5° (*c* 1.00, CH_3OH)). (+)-**1** HCl: $[\alpha]^{25}_D$ +16.2° (*c* 1.00, CH_3OH),[9e] $[\alpha]^{20}_D$ +16.4° (*c* 1.00, CH_3OH),[9c] $[\alpha]^{20}_D$ +16.1° (*c* 1.00, CH_3OH).[9i]

A Convergent Method for the Stereoselective Synthesis of Trisubstituted Alkenes

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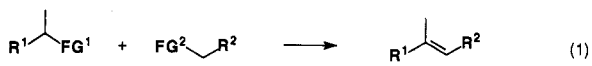
Summary: A method for the stereoselective, convergent synthesis of trisubstituted alkenes has been developed. The procedure features the synthesis of allylic alcohols **9** by coupling an aldehyde with a vinyl organometallic reagent. Treatment of **9** with carbon disulfide and methyl iodide gave the intermediate allylic xanthates **10** that underwent facile [3,3]-sigmatropic rearrangement to give the dithiocarbonates **11** and **12**, radical reduction of which gave the (*E*)-alkenes **13** as the major products.

A common functional element present in a large number of natural products is a trisubstituted carbon–carbon double bond. Consequently, the convergent, stereoselective construction of trisubstituted alkenes constitutes an important problem in synthetic organic chemistry.[1] Indeed, while we were formulating strategies for the total syntheses of several natural products, it became apparent that known methods for coupling two fragments with the stereoselective formation of a trisubstituted double bond according to eq 1 were somewhat limited in scope.[2-5] We therefore set to the task of devising solutions to this problem.



(1)

After considering a number of possible connective routes to alkenes, we concluded that the sequence of reactions

(1) For reviews, see: (a) Faulkner, D. J. *Synthesis* **1971**, 175. (b) Reucroft, J.; Sammes, P. G. *Quart. Rev.* **1971**, *25*, 135.

(2) Wittig and related reactions: (a) Bestmann, H. J.; Vostrowsky, O. *Topics Curr. Chem.* **1983**, *109*, 85. (b) Buss, A. D.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 3931.

(3) Peterson olefination: (a) Ager, D. J. *Org. React.*, in press. (b) Barrett, A. G. M.; Flygare, J. A. *J. Org. Chem.* **1991**, *56*, 638. (c) Barrett, A. G. M.; Hill, J. M.; Wallace, E. M. *J. Org. Chem.* **1992**, *57*, 386.

(4) Julia coupling: (a) For a review, see: Kocienski, P. *Phosphorus Sulfur Relat. Elem.* **1985**, *24*, 97. See also: (b) Hanessian, S.; Ungolini, A.; Dubé, D.; Hodges, P. J.; André, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776. (c) Hirama, M.; Nakamine, T.; Ito, S. *Tetrahedron Lett.* **1988**, *29*, 1197. (d) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368. (e) White, J. D.; Bolton, G. L. *J. Am. Chem. Soc.* **1990**, *112*, 1626.

(5) A variety of complementary methods have been devised for the stereoselective synthesis of trisubstituted olefins. Via coupling of vinylic substrates: (a) Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329. (b) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, *221*. (c) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (d) Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1990**, *31*, 5541. Via carbometalation: (e) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. Via metalate rearrangements: (f) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894. (g) Wadman, S.; Whitby, R.; Yeates, C.; Kocienski, P.; Cooper, K. *J. Chem. Soc., Chem. Commun.* **1987**, 241. (h) Kocienski, P.; Dixon, N. J.; Wadman, S. *Tetrahedron Lett.* **1988**, *29*, 2353. (i) Kocienski, P.; Wadman, S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363; *J. Org. Chem.* **1989**, *54*, 1215. (j) Kocienski, P.; Dixon, N. J. *Synlett* **1989**, *52*. (k) Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933. (l) Stocks, M.; Kocienski, P.; Donald, D. K. *Tetrahedron Lett.* **1990**, *31*, 1637. Via [3,3]-rearrangements: (m) For a review, see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (n) Davidson, A. H.; Eggleton, N.; Wallace, I. H. *J. Chem. Soc., Chem. Commun.* **1991**, 378. From β-Lactones: (o) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176.

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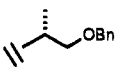
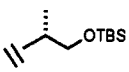
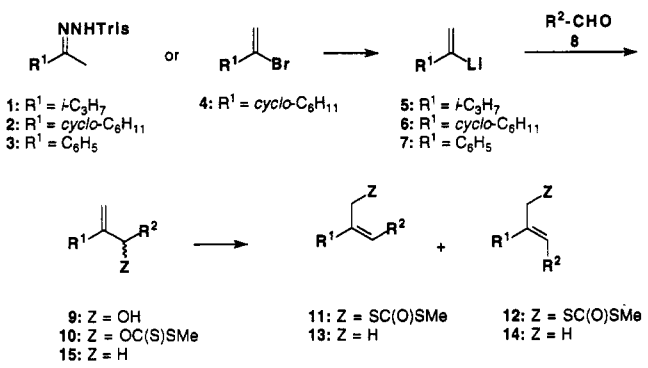
Table I. Convergent Synthesis of Alkenes

entry[a]	R^1	R^2	% yield of 9	% overall yield[a] of 11 and 12 (11:12 ratio)[b]	% overall yield of reduction (13:14:15 ratio)[b]
a	i-C_3H_7–	n-C_6H_{13}–	90	89 (5:1)	90 (11:1:6)
b	c-C_6H_{11}–		65	95 (1.5:1)	89 (9.6:1.2:1) 50[c] (9.6:1.2:1)
c	c-C_6H_{11}–		74	85 (1.4:1)	81 (20:1:1)
d	c-C_6H_{11}–		80	95 (1.2:1)	70 (12:1:1)
e	c-C_6H_{11}–	C_6H_5–	89	93 (2.2:1)	94 (6.5:2:1)
f	c-C_6H_{11}–	$PhCH_2CH_2$–	81	86 (3.5:1)	85 (5:1:3)
g	c-C_6H_{11}–	Ph(Me)CH–			57[c] (5:1:1)
h	C_6H_5–	i-C_3H_7–	84	87 (2.8:1)	84 (50:1:5)

[a] The vinyllithium reagents 5–7 were generated from the corresponding trisylhydrazone (method A).[16] [b] Product ratios were determined by 300- and/or 500-MHz ^1H NMR. [c] The vinyllithium reagent 6 was generated from the corresponding vinyl bromide; yield is overall from the aldehyde (method B).[16]

Scheme I



outlined in Scheme I merited examination.[6] The underlying features of the approach involved the coupling of the two requisite fragments by nucleophilic addition of vinyl anions 5–7 to aldehydes 8 to give a mixture of epimeric allylic alcohols 9. Following conversion of 9 into their respective xanthates 10, we envisioned that a facile [3,3]-sigmatropic rearrangement[7] would provide the corresponding dithiocarbonates, presumably as a mixture of geometric isomers 11 and 12. We anticipated that subsequent scission[8] of the carbon–sulfur bond of 11 and 12 by a tin radical would furnish an intermediate allyl radical that would equilibrate rapidly[9] to the more stable transoid form and deliver 13 as the major product upon reaction with a hydrogen atom source.

Despite precedent for each of the steps in Scheme I, it was not possible to assess a priori the overall chemical and stereochemical efficiency of the process, and a number of critical questions were identified at the outset of our inquiry. For example, the extent to which the stereochemistry of the double bond in the product alkenes depended upon the ratio of geometric isomers of the intermediate dithiocarbonates was unknown. If the geometry of the double bond in 11 and 12 was transferred directly to 13 and 14, respectively, then the stereochemistry of the [3,3]-sigmatropic rearrangement of 10 to give 11 and/or 12 would be important. However, if geometric isomerism of the intermediate allyl radical was fast relative to hydrogen atom transfer, the ratio of 13 and 14 would be independent of the ratio of 11 and 12 and would correlate instead with the degree of preference for the more stable (*E*)-allylic radical. This scenario would lead to the preferential production of 13 irrespective of the isomeric composition of intermediate dithiocarbonates 11 and 12. The stability of the product olefins 13 and 14 under the conditions of the tin hydride mediated reduction would also have to be assessed, since thermodynamic control of the product ratio is a possibility. In addition to these stereochemical issues, there was the regiochemical question of whether hydrogen atom transfer to the intermediate allyl radical that was produced upon reductive scission of 11 and 12 would furnish 15 in addition to 13 and/or 14. To address these issues and to assess the viability of the approach to the synthesis of trisubstituted alkenes as depicted in Scheme I, we executed a series of studies, some of which are presented herein.

In the event, the aldehydes 8 were allowed to react with the vinyl anions 5–7, which were generated from the corresponding 2,4,6-triisopropylbenzenesulfonyl(trisyl)-hydrazones 1–3[10] [*n*-BuLi (2 equiv); −78 → 0 °C; 1 h], to give the allylic alcohols 9 (65–90%). The xanthates 10 formed from the alcohols 9 [(a) NaH, CS_2 (xs); 2 h; rt → 50 °C, 1 h; (b) MeI (xs); 6 h; rt] were not isolated but were converted directly into a mixture of the dithiocarbonates 11 and 12 upon heating in benzene at reflux; the [3,3]-sigmatropic rearrangement occurred slowly at rt. Reductive cleavage of the carbon–sulfur bond in 11 and 12 was then achieved by radical reduction [*n*-Bu_3SnH (3–4 equiv), AIBN, benzene, reflux) to always give 13 as the

(6) For a conceptually related construction, see: Meyers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208.

(7) Harano, K.; Ohizumi, N.; Misaka, K.; Yamashiro, S.; Hisano, T. *Chem. Pharm. Bull.* **1990**, *38*, 619 and references cited therein.

(8) For related processes, see: (a) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708. (b) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130. (c) Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1623.

(9) (a) Korth, H.-G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483. However, see: (b) Walling, C.; Thaler, W. *J. Am. Chem. Soc.* **1961**, *83*, 3877. (c) Menapace, L. W.; Kuivila, H. G. *J. Am. Chem. Soc.* **1964**, *86*, 3047.

(10) (a) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. (b) For a review, see: Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.

(11) The structure assigned to each compound was in full accord with its spectral (^1H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of all new compounds were obtained by recrystallization, flash chromatography, or preparative HPLC or TLC and gave satisfactory identification by high-resolution mass spectrometry. All yields are based on isolated, purified materials.

(12) These mixtures were obtained by partial purification of the mixtures of 11 and 12 by preparative HPLC.

(13) (a) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681. (b) Kulicke, K. J.; Giese, B. *Synlett* **1990**, 91.

major product together with variable quantities of 14 and 15 (see Table I). Somewhat surprisingly, product distributions and yields were not affected by the initial concentration of tri-*n*-butyltin hydride (ca 0.3 M to high dilution) relative to 11 and 12 (0.04–0.08 M) nor by prolonged reaction times. When the vinyllithium reagent 6 was prepared from the vinyl bromide 4[14] [*t*-BuLi (2 equiv); −78 → 0 °C; 0.5 h], a simplified procedure was devised that involved trapping the intermediate lithium alkoxide in situ to provide the corresponding xanthate 10. The resulting crude xanthate was then reduced directly with tri-*n*-butyltin hydride to give 13 and the isomeric alkenes 14 and 15.

The [3,3]-sigmatropic rearrangement of the allylic xanthates 10 appears in each case to give the allylic dithiocarbonates 12 as the major products, although the preference is not always strong. This trend is qualitatively in accord with the prediction that these rearrangements should occur predominantly via the more stable chairlike transition states. The structural assignments for the dithiocarbonates 11 and 12 were based upon examination of ^1H and ^{13}C NMR spectra of the mixtures. Owing to the deshielding that occurs consequent to steric compression with the cis alkyl residue, the protons attached to the methylene group α to sulfur in the minor component 11 of these mixtures appear downfield from those in the major component 12. Consistent with this hypothesis is the additional observation that in the ^{13}C NMR spectra the carbon atom α to sulfur in the minor product is always shifted upfield relative to the carbon in the major isomer; such shielding in the ^{13}C spectra would be a consequence of steric compression (γ effect). In one instance, it was possible to separate the geometric isomers **11b** and **12b** and characterize them individually by ^1H and ^{13}C NMR spectroscopy. The major isomer **12b** exhibited a significant NOE between the vinyl hydrogen and the methylene group α to the sulfur atom, whereas the minor isomer **11b** exhibited an NOE between the vinyl hydrogen and the methylene hydrogens on the cyclohexane. These observations lend further support to our structural assignments.

Since the major products obtained upon radical reduction of the mixtures of 11 and 12 gave the desired (*E*)-alkenes 13 as the major products, there is no meaningful correlation between the stereochemistry of the intermediate allylic dithiocarbonates 11 and 12 with the stereochemical outcome of the radical reduction. In control experiments, mixtures of 11 and 12 that differed in composition from those obtained directly from the rearrangement were subjected to the conditions (i.e., refluxing benzene) that were employed for the radical reduction.[12] Since these ratios did not change, we presume that no thermal isomerization about the double bond of 11 and 12 via reversible [3,3]-sigmatropic rearrangement occurred during the reduction. In another control experiment, we demonstrated that the product olefins 13 and 14 did not isomerize in the presence of tri-*n*-butyltin hydride and AIBN in refluxing benzene. Based upon these observations, it presently appears that (*Z*)- → (*E*)-isomerization of the intermediate allyl radical, which was generated upon reaction of 11 and 12 with tri-*n*-butylstannyl radical, occurs prior to its reduction via hydrogen atom transfer.

Since one might anticipate that the regio- and stereochemical outcome of the hydrogen atom transfer to the allyl radical might be effected by the nature of the hydrogen donor, we briefly surveyed the use of alternative reagents. However, when triphenyltin hydride or tris(trimethylsilyl)silane[13] was employed as hydrogen atom donor, there was no improvement in either the stereo- or regioselectivity. Similarly, homolytic generation of tin radicals from hexamethylditin[15] in the presence of 11 and 12 employing hydrogen atom sources as 1,4-cyclohexadiene offered no improvement.

This new procedure for the convergent synthesis of trisubstituted alkenes proceeds with a significant level of stereoselectivity to furnish the (*E*)-alkenes 13 as the major product. One drawback that surprisingly emerges in certain cases is the concomitant formation of quantities of the disubstituted alkenes 15, which arise from trapping of the intermediate allyl radical at the more substituted terminus. We are presently exploring other variants of this approach in an effort to develop more stereoselective and efficient procedures for effecting this important construction.

Acknowledgment. We thank the National Institutes of Health and the Robert A. Welch Foundation for their generous support of this research.

(14) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

(15) (a) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079. (b) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.

(16) **Preparation of Trisubstituted Alkenes. Method A.** To a solution of the triisopropylbenzenesulfonylhydrazone 1–3 (1.62 mmol) in dry THF (5 mL) under Ar at −78 °C was added dropwise a solution of *n*-BuLi/hexanes (0.8 mL of 4.1 N, 3.3 mmol), and the mixture was stirred at −78 °C for 30 min and then at 0 °C for 15 min. A solution of aldehyde 8 (1.62 mmol) in dry THF (2 mL) was added, and the resulting mixture was warmed to rt over 1 h and stirred for 2 h. Saturated $NaHCO_3$ (5 mL) was added, and the mixture was extracted with Et_2O (3 × 15 mL). The organic layer was washed with saturated NaCl (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford crude 9, which was purified either by distillation or flash chromatography (hexanes/EtOAc). A solution of allylic alcohol 9 (1.3 mmol) in CS_2 (7.5 mL, 9.4 g, 125 mmol) was added to a suspension of NaH (~475 mg, 19.8 mmol) in dry THF (20 mL) at rt. The mixture was stirred for 2 h at rt and for 1 h at 50 °C, whereupon it was cooled to rt. After adding MeI (2.80 g, 19.8 mmol), stirring was continued for 6 h at rt. The mixture was filtered and the solvent removed under reduced pressure. The resulting crude xanthate 10 was dissolved in C_6H_6 (20 mL), and the mixture was heated at reflux for 6 h. After being cooled to room temperature, the solution was concentrated to give a mixture of dithiocarbonates 11 and 12 as a yellow oil. Further purification may be effected using flash chromatography (hexanes/EtOAc), but the crude material thus obtained was sufficiently pure for the next step. To a solution of the crude mixture of dithiocarbonates 11 and 12 (1.06 mmol) in C_6H_6 (15 mL) containing AIBN (30 mg, 0.18 mmol) was added tri-*n*-butyltin hydride (1.05 mL, 1.14 g, 3.92 mmol), and the solution was heated at reflux for 8–10 h. Evaporation of the solvent followed by purification of the residue by flash chromatography (hexane) delivered a mixture of alkenes 13, 14, and 15. **Method B.** To a solution of vinyl bromide 4 (99 mg, 0.52 mmol) in dry THF (4.0 mL) at −78 °C was added dropwise a 1.66 M solution of *t*-BuLi in pentane (0.62 mL, 1.04 mmol). After stirring 20 min at −78 °C, the appropriate aldehyde 8 (0.52 mmol) in THF (0.5 mL) was added. The solution was allowed to warm slowly to rt over 3 h, whereupon CS_2 (0.31 mL, 5.2 mmol, 10 equiv) was added. After 3 h, MeI (0.32 mL, 5.2 mmol) was added. The mixture was stirred for 8 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 10 mL). The combined Et_2O layers were dried ($MgSO_4$0), filtered, and concentrated to provide the crude xanthate 10 (177 mg) as an oil. The crude xanthate thus obtained was dissolved in dry benzene (13 mL), and AIBN (8 mg, 0.05 mmol) and n-Bu_3SnH (616.9 mg, 2.12 mmol) were added. The resulting mixture was heated at reflux for 8 h, whereupon the solution was cooled and the solvent removed under reduced pressure to give an oil that was purified by flash chromatography (hexanes) to give a mixture of 13, 14, and 15.