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A Method for the Net Contra-thermodynamic Isomerization of Cyclic Trisubstituted Alkenes

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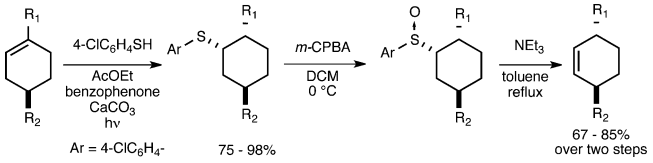
ABSTRACT



A simple sequence for the net contra-thermodynamic isomerization of cyclic trisubstituted alkenes is reported consisting of a radical addition of *p*-chlorothiophenol, followed by oxidation to the sulfoxide and thermal *syn*-elimination to give the least substituted isomeric cycloalkene.

As part of an ongoing project aimed at the synthesis of pseudopteroxazole **1** and other structurally related natural products, we were faced with the difficult task of controlling the relative stereochemistry at C-4 and C-7 (Figure 1). While attempting to overcome this synthetic hurdle, we devised a practical, reasonably general procedure for converting a cyclic trisubstituted alkene into the thermodynamically less stable disubstituted isomer. Our preliminary results are described herein.

Pseudopteroxazole **1** is a diterpenoid alkaloid possessing the amphilectane skeleton found in the pseudopterosins, but where the catechol subunit has been replaced by an uncommon benzoxazole.[1] The amphilectosins have a seco-pseudopterosin structure and were recently shown to be key biosynthetic intermediates.[2] Seco-pseudopteroxazole **3** and erogorgiaene **4** are two other related natural products with the serrulatane backbone. Pseudopteroxazole **1** has a strong inhibitory activity against *Mycobacterium tuberculosis* H37Rv (97% at 12.5 mg/mL).[3]

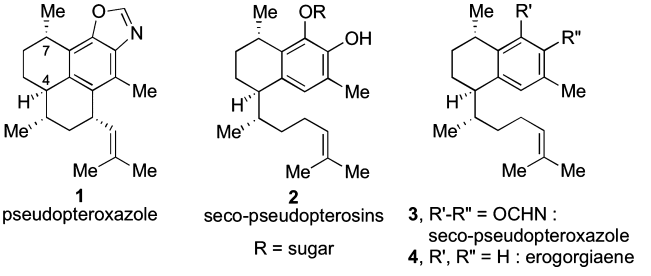


Figure 1. Pseudopteroxazole and related natural products.

The intricate structure of these substances as well as the interesting biological activity profile of several members has elicited sustained synthetic activity in this area over the past two decades.[4]

Our synthetic plan hinged on the use of two successive radical reactions to assemble rapidly most of the serrulatane framework, as illustrated by the model transformations in Scheme 1 (DLP = lauroyl peroxide).[5] The relatively

(1) (a) Rodriguez, A.; Ramirez, C.; Rodriguez, I.; Gonzalez, E. *Org. Lett.* **1999**, *1*, 527. (b) Potts, B. C.; Faulkner, D. J. *J. Nat. Prod.* **1992**, *55*, 1701. (c) Mayer, A. M. S.; Jacobson, P. B.; Fenical, W.; Jacobs, R. S.; Glaser, K. B. *Life Sci.* **1998**, *62*, 401. (d) Duque, C.; Puyana, M.; Narváez, G.; Osorno, O.; Hara, N.; Fujimoto, Y. *Tetrahedron* **2004**, *60*, 10627. (e) Rodríguez, I. I.; Shi, Y. P.; Gracía, O. J.; Rodríguez, A. D.; Mayer, A. M. S.; Sánchez, J. A.; Ortega, E.; González, J. *J. Nat. Prod.* **2004**, *67*, 1672. (f) Roussis, V.; Wu, Z.; Fenical, W. *J. Org. Chem.* **1990**, *55*, 4916. (g) Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140. (h) Ata, A.; Kerr, R. G.; Moya, C. E.; Jacobs, R. S. *Tetrahedron* **2003**, *59*, 4215. (i) Ata, A.; Kerr, R. G.; Moya, C. E.; Jacobs, R. S. *Tetrahedron* **2003**, *59*, 4215. (j) Heckrodt, T. J.; Mulzer, J. *Top. Curr. Chem.* **2005**, *244*, 1.

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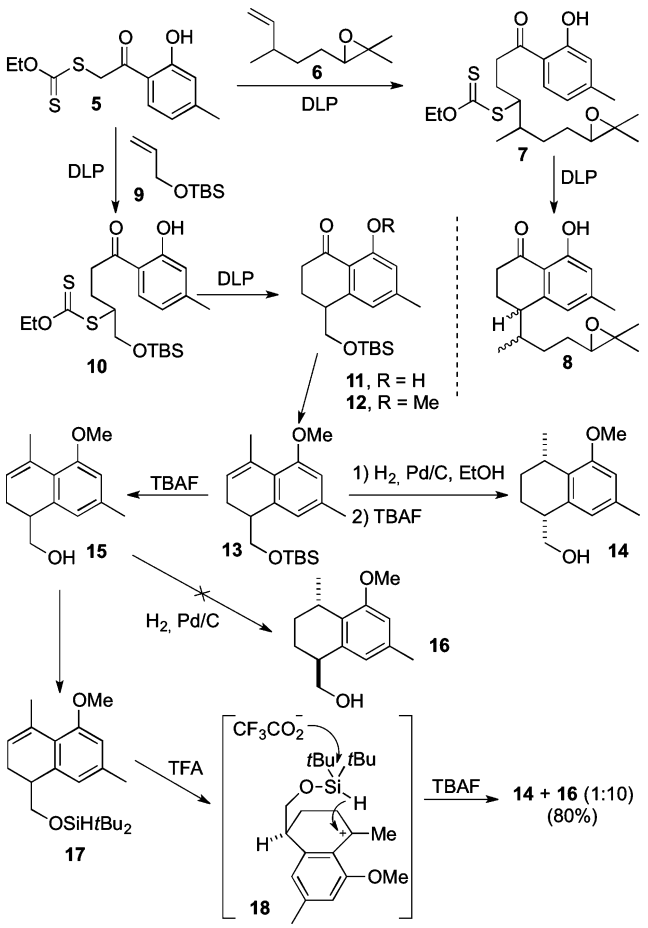
(3) Rodriguez, A.; Ramirez, C. *J. Nat. Prod.* **2001**, *64*, 100.

10.1021/ol4018744

Scheme 1

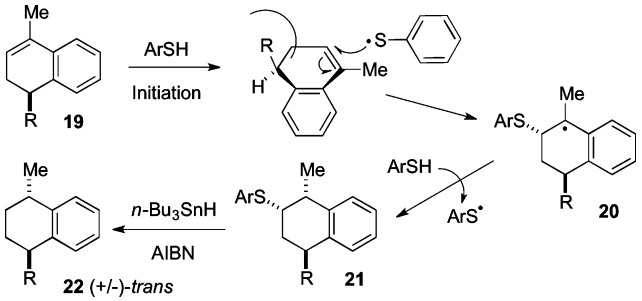


efficient addition and cyclization of xanthate **5** to citronellene derived epoxide **6** to give tetralone **7** crisply encapsulates our strategy and underscores the mild and tolerant nature of the radical process.[5a] The next stage in this study called for developing a way to install the missing methyl group on C-7 with the correct *trans* relationship with respect to the side chain on C-4 (pseudopteroxazole numbering).

The simpler model **13** was readily prepared by the sequence outlined in Scheme 1. Not surprisingly, catalytic reduction furnished the unwanted *cis* derivative **14** through delivery of the hydrogen from the least hindered face of the molecule.[6] Following precedents by Thompson and by Nichols,[7] we attempted the reduction on the free alcohol **15** in a noncoordinating solvent under various conditions, in the hope that the hydroxyl group would chelate the palladium and direct the approach of the hydrogen from the same side and therefore lead to the desired *trans* product **16**. Unfortunately, our efforts were all in vain.

Another, more fruitful approach relied on an elegant procedure devised by McCombie and co-workers,[4l,m] whereby an intramolecular delivery of hydride is accomplished from the correct face by using an internal siloxane. Indeed, exposure of compound **17** to trifluoroacetic acid followed by treatment with tetrabutylammonium fluoride afforded the desired epimer **16** as the major product.

Scheme 2



Having secured one potential solution, we undertook the exploration of a conceptually different and possibly more general route, since it does not require the presence of a well-positioned hydroxyl group on the side chain. Another practical drawback of the internal hydride transfer we sought to avoid is the need to work under high dilution (0.005 M) and to add the trifluoroacetic acid (10 equiv) very slowly over 10 h. In our alternative approach, control of the relative stereochemistry would be achieved by using the presence of the substituent on C-4 to direct the radical addition of a thiol to the alkene in **19** from the opposite side to give intermediate carbon radical **20** (Scheme 2).[8] Because of its proximity, the newly introduced sulfide should exert a greater influence on the course of the hydrogen atom transfer and favor the formation of the desired diastereoisomer **21**. Removal of the sulfide would then complete the sequence.

In the event, the outcome was not as clear-cut as initially hoped. After some experimentation, we found that the

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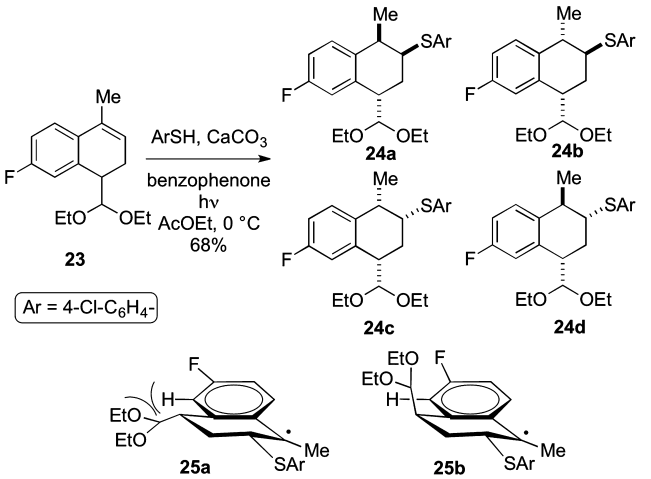
(5) (a) Petit, L.; Zard, S. Z. *Chem. Commun.* **2010**, *46*, 5148. For earlier examples of tetralone formation using xanthate chemistry, see: (b) Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759. (c) Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 3717. (d) Cordero-Vargas, A.; Pérez-Martin, I.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2004**, *2*, 3018. For a review on the degenerative radical addition of xanthates, see: (e) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

(6) Tippett, L. M.; Massywestropp, R. A. *Aust. J. Chem.* **1993**, *46*, 945.

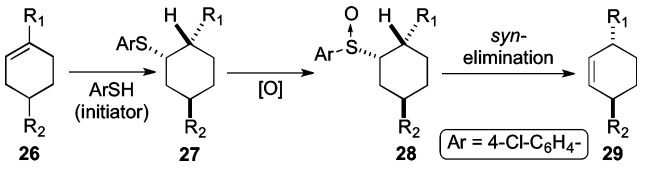
(7) (a) Thompson, H. W. *J. Org. Chem.* **1971**, *36*, 2577. (b) Chambers, J. J.; Parrish, J. C.; Jensen, N. H.; Kurrasch-Orbaugh, D. M.; Marona-Lewicka, D.; Nichols, D. E. *J. Med. Chem.* **2003**, *46*, 3526.

(8) For a recent review on the radical addition of thiols to alkenes, see: Hoyle, C. E; Bowman, C. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540.

Scheme 3



Scheme 4



radical addition of the thiol was best accomplished photochemically using visible light and benzophenone as the photoinitiator. While the chemical yield of the addition was satisfactory, the stereoselectivity was only moderate albeit in the desired direction. A typical example is displayed in Scheme 3. Thus, irradiation with a tungsten-halogen lamp of a solution of **23** and benzophenone in ethyl acetate at 0 °C furnished a 1.0:0.39:0.14:0.05 ratio of isomers **24a**–**d** in a combined yield of 68%.

Attempts to improve the stereoselectivity by modifying the steric bulk of the thiol or that of the side chain either had only a marginal effect or resulted in a poor chemical yield. To further complicate matters, the various diastereoisomers were essentially inseparable by normal column chromatography. Clearly, in the present case, the opposing steric effects of the sulfide group and the side chain on C-4 were of comparable magnitude, resulting in the formation of only moderately interesting isomeric mixtures. One possible explanation is that the arylthiyl group occupies a pseudoequatorial position, whereas the diethoxymethyl side chain prefers a pseudoaxial disposition as in **25b** in order to relieve the allylic strain due to repulsion with the neighboring aromatic hydrogen present in **25a**.[6] This axial orientation causes a significant shielding of the β-face and counteracts the directing effect of the arylthiyl group.

Nevertheless, the addition of a thiol to cyclic trisubstituted alkenes could be more usefully stereoselective in other structures, and this indeed would furnish a practical

Table 1. Net Contra-thermodynamic Isomerization of Cycloalkenes

cycloalkenes **26**	sulfides **27** (*cis*:*trans*) Ar = 4-ClC$_6$H$_4$-	oxidation/elimination
26a	**27a** 89% (94:6)	**29a** 76% (95:5)
26b	**27b** 96% (98:2)	**29b** 83% (97:3)
26c	**27c** 95% (96:4)	**29c** 85% (96:4)
26d	**27d** 98% (91:9)	**29d** 84% (91:9)
26e	**27e** 86% (87:13)	**29e** 84% (88:12)
26f	**27f** 87% (71:29)	**29f** 63% (from pure *cis*)
26g	**27g** 95% (75:25)	**29g** 71% (75:25)
26h	**27h** 91% (87:13)	**29h** 84% (88:12)
26i	**27i** 92% (100:0)	**29i** 71% (100:0)
26j	**27j** 92% (71:29)	**29j** 78% (69:31)
26k	**27k** 75% (100:0)	**29k** 70% (100:0)
26l	**27l** 72% (91% brsm) (95:5)	**29l** 67% (96:4)

method for the isomerization of trisubstituted cyclic alkenes into the thermodynamically less stable isomers. This conjecture is summarized in Scheme 4. Thus, the overall *anti* addition of *p*-chlorothiophenol to the requisite

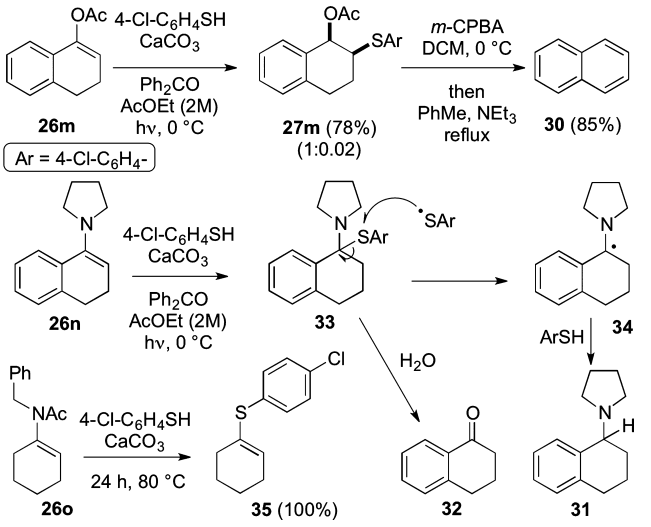
cycloalkane **26** should give rise to sulfide **27** as the major product. Oxidation would lead to a sulfoxide **28** that can *syn*-eliminate *only from the methylene side* and not from the methine side, since the hydrogen atom in the latter case is on the *opposite side of the ring* and cannot therefore participate in a *syn*-elimination. The choice of *p*-chlorothiophenol was dictated by the fact that it is crystalline at room temperature, cheap, and much less difficult to handle than the parent thiophenol.

We tested this sequence on a number of different structures. Our results are collected in the Table 1. Fused dihydronaphthalenes and one example of a benzocycloheptene were successfully isomerized, as indicated by examples **29a**–**g**. 1-*p*-Methoxyphenyl-cyclopentene, -cyclohexene, and -cycloheptene could also be isomerized (examples **29h**–**j**). In the last case, the stereoselectivity was only modest, presumably because of the greater flexibility of the ring and the consequent diminished differentiation of the two faces. It must be remembered that the hydrogen atom transfer process from thiols is an exceedingly fast process with a relatively early transition state and consequently a lesser sensitivity to steric hindrance.[9] Finally, cyclohexene derivatives lacking an aromatic substituent (which normally facilitates the radical addition step) were shown to be also viable substrates, as demonstrated by examples **29k**–**l**. The isomeric ratio indicated for compounds **29a**–**l** reflects as expected the diastereoisomeric ratio of the precusor sulfides **27a**–**l**.

In the case of enol acetate **26m**, the radical addition was efficient but the alkene arising from elimination of the sulfoxide underwent spontaneous aromatization to naphthalene **30** under the reaction conditions (Scheme 5). Interestingly, enamine **26n** led to a 4:1 mixture of the tertiary amine **31** and the hydrolyzed product **32**. The reduced product **31** presumably arises from the Markovnikov addition of the thiol onto the electron-rich enamine followed by the homolytic cleavage of the newly formed carbon–sulfur bond and reduction of the corresponding radical (Scheme 5). Unfortunately, the addition of a base did not prevent this reaction. Finally, *N*-acetylenamine **26o** underwent quantitative transformation into vinyl sulfide **35**, most likely by Markovnikov addition followed by elimination of *N*-benzylacetamide. The latter could be

(9) The rate constant for hydrogen atom abstraction from thiophenol by a carbon centered radical is of the order of 10^8 M^{-1} s^{-1}: (a) Newcomb, N.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275. (b) Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268.

Scheme 5



observed in equimolar amounts in the NMR spectrum of the crude reaction mixture.

In summary, we have described a straightforward, mild method for converting a cyclic trisubstituted alkene into the less stable disubstituted isomer, using cheap and readily available reagents. Such net contra-thermodynamic shifts of an alkene in a ring would normally require multistep sequences, such as an anti-Markovnikov hydration via hydroboration–oxidation followed by tosylation or mesylation of the resulting alcohol and E2 elimination (the photodeconjugation of enones is, however, one important exception). Many of the isomerized cycloalkenes in Table 1 would be very difficult to obtain by other routes, especially the rather sensitive 1,4-dihydronaphthalenes. Indeed, the possibility of accessing less stable cycloalkenes allows for synthetic planning not hitherto practical.

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Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.