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Tetrahedron Letters 47 (2006) 2747–2750
Tetrahedron Letters

A short and convenient access to a *trans*-hydrindane unit from the *anti-meso*-acetylmethyldivinylcyclopentane via a radical pathway

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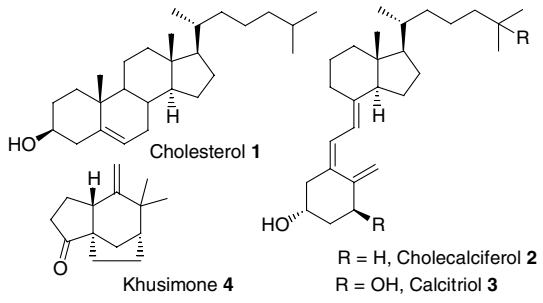
Received 25 January 2006; revised 9 February 2006; accepted 14 February 2006
Available online 2 March 2006

Abstract—An efficient route for multigram synthesis of a *trans*-hydrindane unit, involving a selective *6-endo-trig* α-carbonyl radical cyclization of the α-xanthyl ketone **10** derivating from the *anti-meso*-acetylmethyldivinylcyclopentane **9** through a xanthate group transfer, is achieved in good yield. Preparation of an advanced intermediate for the Julia–Kocienski coupling, used in the elaboration of the trienic system of vitamin D (or calciferol) analogs, was materialized by conversion of the xanthate moiety to a 2-benzothiazole sulfonyl group.

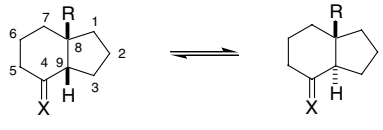
trans-Hydrindane systems are key substructures of several bioactive natural products, such as terpenes,[1] steroids,[2,3] vitamin D, and their related metabolites,[4,5] that have stimulated intense synthetic interests over the last few years due to their pronounced biological activities.[6] Although different strategies have been developed to achieve their elaboration, efficient and straightforward approaches to polyfunctionalized *trans*-bicyclo[4.3.0] nonane units still remain desirable and represent a challenging synthetic purpose for organic chemists (Scheme 1).[7]

The construction of the *trans*-ring junction has proven to be an awkward synthetic problem partly due to the relative stability of *cis–trans* hydrindanes according to the substitution with alkyl groups and carbonyl functions.[8] Calculations suggest that the *trans*-isomer is more stable than the *cis* whereas introduction of a methyl substituent at the C-8 position causes an energy difference between both isomers such that the *cis* becomes more stable by 0.98–1.23 kcal/mol than its trans counterpart.[9] Steroidal *trans*-8-methyl-4-hydrindanones, such as the Grundman–Windaus ketone obtained from ozonolysis of vitamin D_3, turned out to be less stable than the *cis* form by approximately 1.45–2.36 kcal/mol.[8b,9,10] Indeed, the *trans*-ring junction can be easily epimerized under acidic or basic conditions (Scheme 2).[11]



Scheme 1.

As part of a program directed toward the synthesis of calciferol analogs,[12] we were interested in developing a concise, flexible, and practical synthetic method for the preparation of *trans*-hydrindane bicyclic subunits and related compounds. This methodology will have to prevent any isomerization of the trans-ring junction and



R = H; X = H_2, ΔE = −0.31 to −1.17 kcal/mol
R = Me; X = H_2, ΔE = +0.98 to +1.23 kcal/mol
R = Me; X = O, ΔE = +1.45 to +2.36 kcal/mol

Scheme 2.

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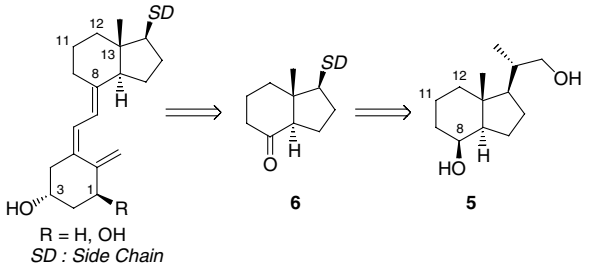
doi:10.1016/j.tetlet.2006.02.076

offer new possibilities for the functionalization of C-11 and C-12 vitamin D positions.[13]

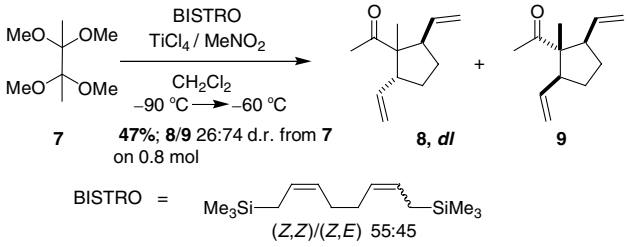
At the present time, fragments that participate to the elaboration of these analogs in most cases derive from the Inhoffen–Lythgoe diol **5**,[14] obtained by reductive ozonolysis of the expensive vitamin D_2 or ergocalciferol. Introduction of the side chain followed by oxidation of the C-8 position lead to the Grundman–Windaus type ketone **6** which can be coupled with an appropriate A-ring to generate the trienic system (Scheme 3).[5] However, some potential isomerization problems inherent to the structure of *trans*-4-hydrindanones make this strategy unreliable[11,15] and C-11 and C-12 carbon centers less accessible for subsequent derivatizations of these positions.

In connection with our interest in steroid synthesis, we have previously shown that reaction of 2,2,3,3-tetramethoxybutane with 1,8-bis(trimethylsilyl)-2,6-octadiene (BISTRO) in the presence of titanium tetrachloride led to a mixture of *dl*- and *anti-meso*-acetylmethyldivinylcyclopentane **8** and **9** (Scheme 4).[16]

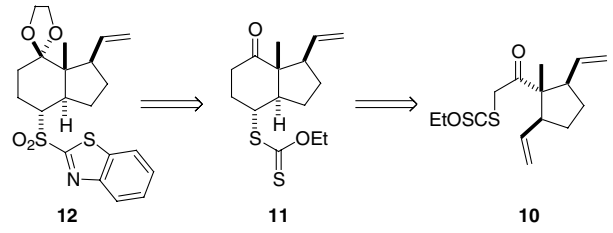
To expand the synthetic utility of this versatile building block, we propose to study the radical cyclization of the xanthate **10** involving a group transfer process extensively developed by Zard and co-workers,[17,18] that should provide a rapid access to *trans*-hydrindanes **11** as precursors of vitamin D analogs (Scheme 5). After a few transformations, this approach should furnish a suitable fragment **12** for the construction of the trienic part by using a Julia–Kocienski olefination coupling as reported in the literature (Scheme 6),[19] without any risk of isomerization of the trans-ring junction of the hydrindane. The presence of the carbonyl group in C-12 should allow the functionalization of C-11 and C-12 carbon centers.[13]



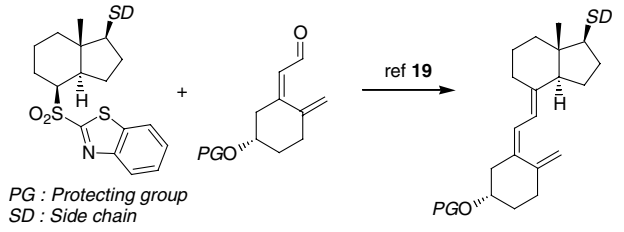
Scheme 3.



Scheme 4.



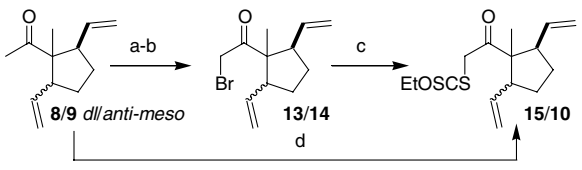
Scheme 5.



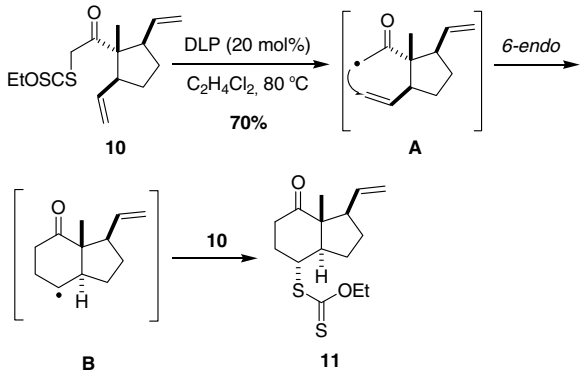
Scheme 6.

With the building block **9** in hand, we envisaged its functionalization in acetyl xanthate derivative **10** by either α-bromination of the ketone moiety followed by nucleophilic displacement of the bromine atom with potassium *O*-ethyl xanthogenic salt or a more straightforward route involving enolate trapping with diethyl bisdithiocarbonate $(SC(S)OEt)_2$. Thus, treatment of **8** and **9**, taken separately or as a mixture,[20] successively with TMSOTf/Hünig's base/CH_2Cl_2 and NBS/$NaHCO_3$/THF at −78 °C gave the bromides **13** or/and **14** (68–76%), which were placed in the presence of an excess of KSC(S)OEt in acetone liberating the xanthates **15** or/and **10** (68–82%).[18a] However, the latter can be readily prepared in 75% yield by quenching the lithium enolate of **8** and **9** with $(SC(S)OEt)_2$ (Scheme 7).[21]

Exposure of the *anti-meso* xanthate **10** to lauroyl peroxide (DLP) (20 mol % added portionwise), as an initiator, in degassed dichloroethane at reflux furnished the unique *trans*-hydrindanone **11** in 70% yield. Its formation can be rationalized by the following mechanism outlined in Scheme 8 where the α-carbonyl radical **A**, generated from **10** during the initiation step by action of a lauroyl radical, undergoes a selective 6-*endo-trig* cyclization with one of both vinyls. Indeed, as reported in the literature, acyclic 2-oxo-5-hexenyl radicals have been shown to evolve through a preferential 6-*endo-trig* cyclization pathway leading to the corresponding cyclohexanones.[22]



Scheme 7. Reagents and conditions: (a) TMSOTf/DIPEA/CH_2Cl_2/−78 °C; (b) NBS/$NaHCO_3$/THF/−78 °C, **13/14** (68–76% over two steps); (c) KSC(S)OEt/acetone/rt, **15/10** (68–82%); (d) (i) LDA/THF/−78 °C; (ii) $(SC(S)OEt)_2$/−78 °C **15/10** (75% over two steps).



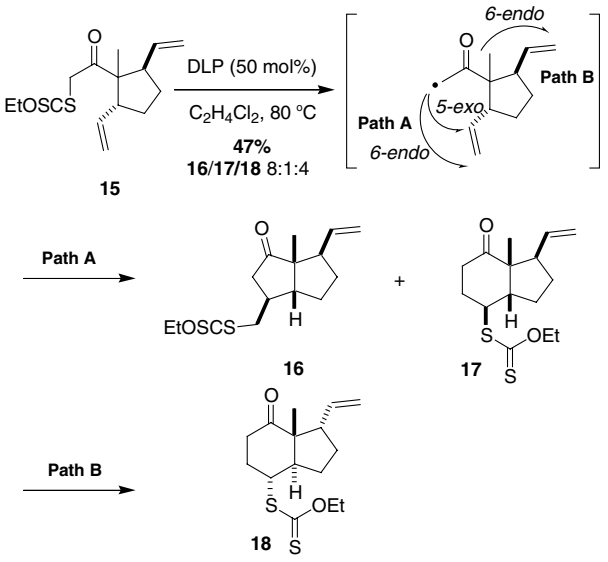
Scheme 8.

MM2 Calculations investigated by Houk match the experimental results and confirm this unexpected regioselectivity of the radical cyclization.[23] Thus, the transient secondary radical **B** can propagate the radical chain by xanthate group transfer. The stereoselectivity of the xanthate moiety at the C-4 position, confirmed by ^{1}H NMR and NOESY experiments, is modulated by the 1,3-diaxial interaction with the angular methyl at C-8 favoring an equatorial attack of the radical **B** onto the xanthate group of another molecule of **10** during the chain process.

The cyclization procedure was next extended to the *dl*-isomer **15**. In this case, **15** has to be treated with a large amount of DLP (50 mol %) for the completion of the reaction. Surprisingly, a significant quantity of 5-*exo*-*trig* and *cis*-fused bicyclic cyclization product **16** was obtained as a unique diastereomer whose relative stereochemistry was corroborated by NOESY experiments, along with the 6-*endo*-*trig* compound **17** in an 8:1 ratio and with a moderate yield (path A). Presence of the adduct **18**, resulting from a 6-*endo*-*trig* closure with the other vinyl substituent in a *trans* relationship with the acetyl group and leading to a *trans*-fused compound, was also detected without any trace of the corresponding 5-*exo*-*trig* cyclization product (path B) (Scheme 9). This inversion of selectivity giving a *5-exo*/*6-endo* ratio of 8:5 in favor of the five-membered ring formation remains unexplained for the moment. Its rationalization by calculation is still under study and will be discussed in a future full-paper.

To avoid the difficult separation of each *dl*- and *anti-meso*-acetylmethyldivinylcyclopentane **8** and **9** on a multigram scale,[20] the cyclization reaction was directly performed on the mixture of isomers **15** and **10** (20 mmol, 26:74 *dl*/*meso*) and gave by consequence both separable products **11** and **16** in 71% yield and a 4:1 ratio, together with only traces (<5%) of **17** and **18**.

Next, our attention turned to the functionalization of **11**. Preparation of an advanced intermediate for the Julia–Kocienski coupling, used in the elaboration of the trienic system for vitamin D analog synthesis, was to be accomplished through conversion of the xanthate moiety to a 2-benzothiazole sulfonyl (Bts) group. The



Scheme 9.

ketone was first protected as its ethylene ketal and subjected to ethylene diamine in ethanol to liberate **19** as a free thiol.[24] Deprotonation of the thiol with sodium hydride in THF and subsequent reaction with 2-chlorobenzothiazole generated the corresponding 2-thiobenzothiazole adduct **20** (63%),[25] which was oxidized with $(NH_4)_6Mo_7O_{24}$ (cat.)/H_2O_2/EtOH to give the sulfonyl derivative **12** (80%, structure by X-ray, Fig. 1, Scheme 10).[19]

In conclusion, this approach represents a simple, efficient and flexible route to *trans*-hydrindane units from the *anti-meso*-acetylmethyldivinylcyclopentane, that can be applicable and useful for the construction of vitamin D analogs. Further modifications such as extension and functionalization of the side chain, and access to both enantiomers are currently in progress. These new building blocks could be coupled with suitable A-rings to prepare new vitamin D analogs.

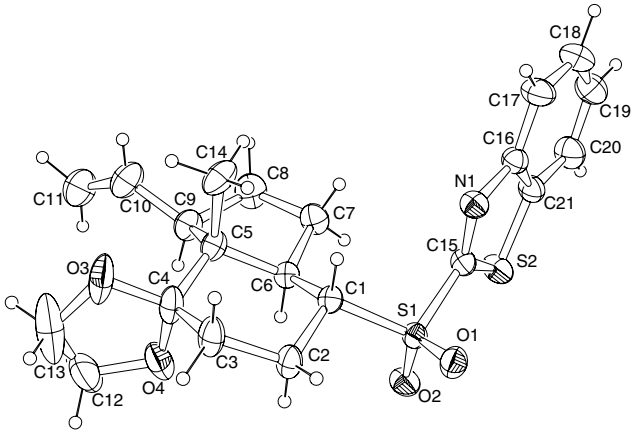
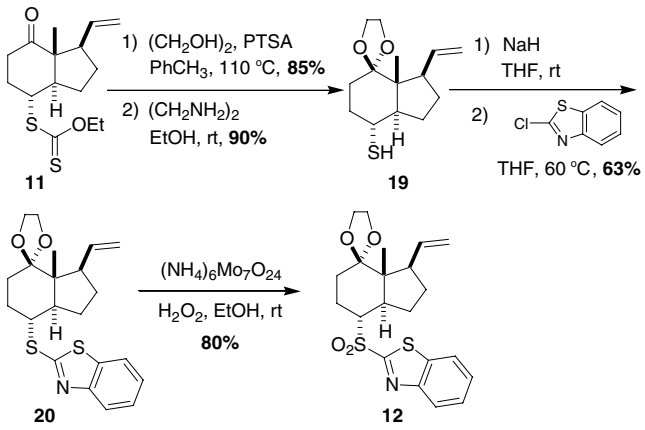


Figure 1. ORTEP drawing of X-ray structure of **12** with labeled heteroatoms. Thermal ellipsoids are scaled to 30% probability level. Hydrogen atoms are drawn to an arbitrary scale.



Scheme 10.

Acknowledgements

We are grateful to the Centre National de la Recherche Scientifique (CNRS) and the Ministère de l'Education Nationale, for the financial support. A.-S.C. is grateful to the 'Région Provence-Alpes-Côte d'Azur' and the CNRS, for a Grant. We are indebted to Professor M. Bertrand, Dr. S. Gastaldi (UMR 6517) and Dr. B. Vacher (Pierre Fabre Medicaments), for helpful comments.

References and notes

1. (a) *Terpene*; Breitmaier, E., Ed.; VCH Verlagsgesellschaft: Germany, 2005; (b) *Carbocyclic Construction in Terpene Synthesis*; Ho, T. L., Ed.; John Wiley & Sons, 1988.
2. *Steroids*, 3rd ed.; Fieser, L. F., Fieser, M., Eds.; Reinhold: New York, 1959.
3. (a) *Steroid Reactions*; Djerassi, C., Ed.; Holden-Day: San Francisco, 1963; (b) *Total Steroid Synthesis*; Akhrem, A. A., Titov, Y. A., Eds.; Plenum Press: New York, 1970; (c) *Total Steroid Synthesis*; Blickenstaff, R. T., Ghoosh, A. C., Wolf, G. C., Eds.; Academic Press: New York, 1974.
4. (a) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; New York: Academic Press, 1997; (b) *Vitamin D Endocrine System: Structural, Biological, Genetic and Clinical Aspects*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Vitamin D Workshop: University of California Riverside: Riverside, CA, 2000.
5. For reviews on various synthetic approaches to vitamin D and its analogs, see: (a) Pardo, R.; Santelli, M. *Bull. Soc. Chim. Fr.* **1985**, 98; (b) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383; (c) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877; (d) Posner, G. H.; Kahraman, M. *Eur. J. Org. Chem.* **2003**, 3889.
6. (a) *Medicinal Chemistry of Steroids*; Zeelen, F. J., Ed.; Elsevier: Amsterdam, 1990; (b) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200; (c) Beckman, M. J.; DeLuca, H. F. In *Prog. Med. Chem.*; Ellis, G. P., Luscombe, D. K., Oxford, A. W., Eds.; Elsevier: Amsterdam, 1998; Vol. 35, p 1.
7. For a well-documented review on *trans*-hydrindane synthesis, see: Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071.
8. (a) Pardo, R.; Archier, P.; Santelli, M. *Bull. Soc. Chim. Fr.* **1986**, 760–765; (b) Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, 2911.
9. Allinger, N. L.; Tribble, M. T. *Tetrahedron* **1972**, *28*, 1191.
10. Lo Cicero, B.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914.
11. (a) Quinkert, G. *Experientia* **1957**, *13*, 381; (b) Inhoffen, H. H.; Quinkert, G.; Schutz, S.; Dampe, D.; Domagk, G. F. *Chem. Ber.* **1957**, *90*, 664.
12. (a) Rodriguez, R.; Ollivier, C.; Santelli, M. *Tetrahedron Lett.* **2004**, *44*, 2289; (b) Rodriguez, R.; Ollivier, C.; Santelli, M. *Synlett* **2006**, 312.
13. Gonzalès-Avión and Mouriño showed that different substituents at the C-12 position increased to 4.4 times the affinity of the related calcitriol analogs for the vitamin D receptor (VDR). Gonzalès-Avión, X. C.; Mouriño, A. *Org. Lett.* **2003**, *5*, 2291.
14. Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2608.
15. For isomerization problems reported in the literature, see: Peterson, P. E.; Breedlove Leffew, R. L. *J. Org. Chem.* **1986**, *51*, 1948.
16. (a) Tubul, A.; Santelli, M. *Tetrahedron* **1988**, *44*, 3975; (b) Pellissier, H.; Faure, R.; Santelli, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1847; (c) Mariet, N.; Pellissier, H.; Ibrahim-Ouali, M.; Santelli, M. *Eur. J. Org. Chem.* **2004**, 2679(d) Unpublished results: Reaction performed on multigram scale (0.8 mol of **7**) gave **8** and **9** in 47% yield and with a 26:74 *dl*/*meso* ratio.
17. For reviews on the chemistry of xanthates, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672; (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur Silicon* **1999**, *153–154*, 137; (c) Zard, S. Z. In *Radical in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M., Eds.; Wiley-VCH GmbH: Weinheim, Germany, 2001.
18. For examples of cyclization of an α-carbonyl radical generated from the corresponding xanthate, see: (a) Bacqué, E.; Pautrat, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 325; (b) Briggs, M. E.; El Qacemi, M.; Kalaï, C.; Zard, S. Z. *Tetrahedron Lett.* **2004**, *45*, 6017.
19. Blakemore, P. R.; Kocienski, P. J.; Marzcak, S.; Wicha, J. *Synthesis* **1999**, 1209.
20. Both *dl*- and *anti-meso*-acetylmethyldivinylcyclopentanes **8** and **9** are particularly difficult to separate by liquid chromatography or distillation on multigram scale. These problems were already reported on small quantities: Pellissier, H.; Santelli, M. *Tetrahedron* **1996**, *52*, 9093.
21. Ester and malonate xanthate derivatives have been reported to be synthesized by reaction of their respective enolates with diethyl bisdithiocarbonate in 50–58% yield. Maslak, V.; Čeković, Ž.; Saičić, R. N. *Synlett* **1998**, 435.
22. (a) Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1520; (b) Porter, N. A.; Chang, V. H.-T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554; (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
23. Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651.
24. (a) Mori, K.; Nakamura, Y. *J. Org. Chem.* **1969**, *34*, 4170; (b) Boivin, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 6877.
25. Chen, C. H. *J. Heterocycl. Chem.* **1976**, *13*, 1079.