Stereoselective Preparation of Vitamin D Precursors Using the Intramolecular Coupling of Alkynes and Cyclopropylcarbene−Chromium Complexes: A Formal Total Synthesis of (±)-Vitamin D_3

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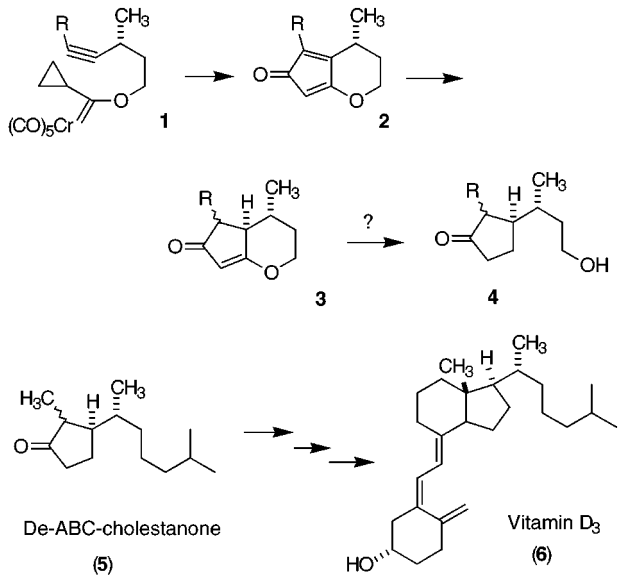
The intramolecular coupling of alkynes and cyclopropylcarbene−chromium complexes has been examined. Complexes that feature a stereogenic center at the propargylic position of the alkyne−carbene tether are the focus of this paper. The reaction produces a cyclopentadienone intermediate fused to an oxygen heterocycle, which is reduced to the corresponding cyclopentenone under the reaction conditions (100 °C in 1% aqueous toluene). The preexisting stereogenic center has a powerful influence on the reduction of the cyclopentadienone ring, and predominantly a single diastereomer is produced in the reaction. Reductive cleavage of the heterocyclic ring with retention of stereochemistry affords compounds featuring a stereocenter on the five-membered ring and on a side chain. Use of the above reaction processes for the synthesis of the vitamin D precursor de-ABC-cholestan-14-one is also discussed.

Introduction

The intramolecular coupling of alkynes and cyclopropylcarbene complexes affords cyclopentenones fused to oxygen heterocycles (e.g., **3**, Scheme 1) in good-excellent yield[2] by way of an unstable cyclopentadienone intermediate (e.g. **2**).[3] As noted in some cases,[2] if a stereogenic center is present in the tethering chain, the heterocyclic ring can be constructed in a stereoselective fashion since the preexisting stereocenter can control the cyclopentadienone reduction event. Acyclic stereocenters adjacent to cyclopentane rings (featured in compound **4**) are a common structural feature for a variety of biologically important natural products (most notably steroids and steroid derivatives), and this class of compounds could result from reductive ring opening of vinylogous ester derivative **3**.[2b,4] Unique in this approach for stereoselective steroid side-chain construction[5] is that the stereogenic center in the carbene complex ultimately controls *all* of the other stereocenters in the five-membered ring. This stereogenic center corresponds to the acyclic stereogenic center for steroid derivatives.

Scheme 1



In this paper, examination of thermolysis reactions for alkyne−carbene complexes containing propargylic stereocenters, further discussion of the cyclopentadienone reduction event, and development of a procedure for reductive opening of the heterocyclic ring in vinylogous

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(2) (a) Herndon, J. W.; Matasi, J. J. *J. Org. Chem.* **1990**, *55*, 786−788. (b) Herndon, J. W.; Matasi, J. J. *Tetrahedron Lett.* **1992**, *33*, 5725−5728.

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(4) Watt, D. S.; McKenna, M. J.; Spencer, T. A. *J. Org. Chem.* **1967**, *32*, 2674−2678.

(5) Construction via ring opening of norbornane derivatives: (a) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378−4380. (b) Grieco, P. A.; Takigawa, T.; Moore, D. R. *J. Am. Chem. Soc.* **1979**, *101*, 4380−4381. (c) Stevens, R. V.; Lawrence, D. S. *Tetrahedron* **1985**, *41*, 93−100. (d) Shimizu, I.; Matsuda, N.; Noguchi, Y.; Zako, Y.; Nagasawa, K. *Tetrahedron Lett.* **1990**, *31*, 4899−4902. Construction via stereoselective enolate alkylation: (e) Clase, J. A.; Money, T. *Can. J. Chem.* **1992**, *70*, 1537−1544. (f) Daniewski, A. R.; Warchol, T. *Liebigs Ann. Chem.* **1992**, 965−973. Construction via stereoselective addition to exo-alkylidenecyclopentane derivatives: (g) Batchco, A. D.; Berger, D. E.; Davoust, S. G.; Wovkulich, P. M.; Uskoković, M. R. *Helv. Chim. Acta* **1981**, *64*, 1682−1687. (h) Hatekeyama, S.; Numata, H.; Takano, S. *Tetrahedron Lett.* **1984**, *25*, 3617−3620. (i) Takahashi, T.; Yamada, H.; Tsuji, J. *J. Am. Chem. Soc.* **1981**, *103*, 5259−5261. Construction via stereoselective Michael addition: (j) Haynes, R. K.; Stokes, J. V.; Hambley, T. W. *J. Chem. Soc., Chem. Commun.* **1991**, 58−60. (k) Grzymacz, P.; Marczak, S.; Wicha, J. *J. Org. Chem.* **1997**, *62*, 5293−5298. (l) Pen, L.-R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1469−1472. Construction via stereoselective hydrolysis−ring opening of an enamine−cyclobutene derivative: (m) Desmaele, D.; Ficini, J.; Guingant, A.; Touzin, A. M. *Tetrahedron Lett.* **1983**, *24*, 3083−3087. Construction via stereoselective Claisen rearrangement: (n) Chapleo, C. B.; Hallett, P.; Lythgoe, B.; Waterhouse, I.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1211−1218.

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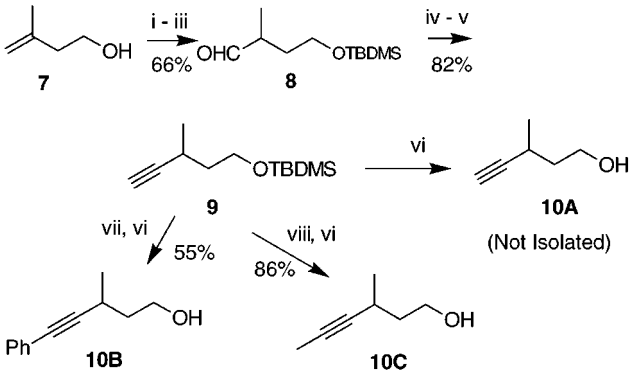
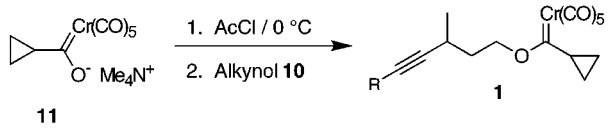
Scheme 2[a]



[a] Key: (i) TBDMSCl; (ii) BH_3−THF, then $NaOH/H_2O_2$; (iii) $(ClCO)_2$/DMSO; (iv) CBr_4/PPh_3; (v) 2 equiv of *n*-BuLi, (vi) $BF_3{\cdot}OEt_2$; (vii) PhI/Pd catalyst; (viii) *n*-BuLi, then CH_3I.

Scheme 3



1A, R = H, 40%; **1B**, R = Ph, 69%; **1C**, R = CH_3, 71%

ester **3** will be discussed. Application of these reactions for the synthesis of (±)-de-ABC-cholestan-14-one (**5**),[6] a synthetic precursor to vitamin D_3 derivatives,[7,8] will be discussed. Vitamin D_3 and various synthetic derivatives display a diverse range of biologically activity, including regulation of calcium, treatment of psoriasis, treatment of breast cancer, and regulation of hormonal responses.[9]

Results and Discussion

Preparation of Alkynol Starting Materials. Alkynol **10A** was prepared from commercially available 3-methyl-3-buten-2-ol according to the synthetic route in Scheme 2. The protected terminal alkyne **9** was transformed to the phenylacetylene derivative via palladium-catalyzed coupling with iodobenzene or to the methylacetylene derivative by deprotonation and alkylation with methyl iodide. Conversion of alkynols to the corresponding cyclopropylcarbene complexes was accomplished through the acetoxycarbene route (Scheme 3)[10] and proceeded in about 70% yield. Due to volatility problems, an ether solution containing crude alkynol **10A** (from silyl ether cleavage) was used directly for the carbene complex

Scheme 4

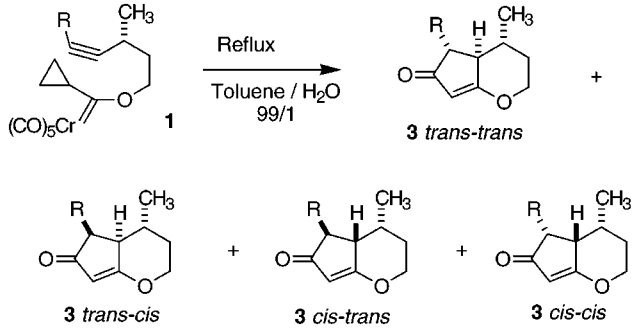


Table 1. Stereoselectivity in the Thermolysis of Alkyne−Carbene Complexes 1A−C

R[a]	yield of **3**[b]	ratio[c]	major isomer of **3**[d]	second most abundant isomer of **3**[d]	stereoselectivity for the heterocyclic ring
H (**1A**)	57	94:6	*trans*	*cis*	94:6
Ph (**1B**)	72	84:9:7	*trans-trans*	*cis-trans*	91:9
CH_3 (**1C**)	70	90:5:5	*trans-trans*	N/A[e]	95:5

[a] The suffixes **A**, **B**, and **C** define the R groups for compounds **1**−**3** and **10**. [b] Combined yield of all stereoisomers. [c] The ratio was determined by integration of the alkene protons in the region δ 5.2−5.4 of the crude reaction mixture. [d] The first stereochemical label refers to heterocycle stereochemistry and the second refers to carbocycle stereochemistry. [e] The minor isomers are equally abundant.

synthesis, and this may account for the low yield in this case. In the other cases, the purified alkynol was employed.

Thermolysis of Alkyne-Carbene Complexes. Carbene complexes **1A**−**C** were heated in refluxing 99/1 toluene/water to effect the cycloaddition/cyclization reaction. In all cases, the expected β-alkoxycyclopentenone derivatives were produced in good yield (combined yield of all stereoisomers) and with a high degree of stereoselectivity (Scheme 4 and Table 1). Contrary to intramolecular terminal alkyne−carbene couplings conducted in dioxane or THF,[2a,10] thermolysis of carbene complex **1A** proceeds in respectable yield. Only three out of the four possible stereoisomers were obtained during thermolysis of the internal alkynes **1B** and **1C**. The major isomer in all cases was assigned as the compound having the trans arrangement of substituents on the heterocyclic ring. For cyclopentenones derived from internal alkynes (**3B** and **C**), the major isomer also features the trans arrangement of substituents in the carbocyclic ring.

Assignment of Stereochemistry. The stereochemistry in the heterocyclic ring for all of the major isomers in Table 1 was assigned as trans on the basis of the large value for the coupling constant between the allylic hydrogen and the hydrogen next to the methyl group (11.4, 11.0, and 11.1 Hz in **3A**-*trans*, **3B**-*trans-trans*,[11] and **3C**-*trans-trans*, respectively). A minor isomer assigned as a cis heterocycle features a considerably smaller value for this coupling (7.8 Hz in **3B**-*cis*−*trans*). The larger coupling observed for the trans heterocycles is more consistent with the diaxial coupling anticipated for this isomer. The stereochemistry in the carbocyclic rings for the major isomers of **3B** and **3C** was assigned as trans on the basis of the smaller coupling between the allylic

(6) For the latest synthesis, see: Pen, L.-R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1473−1474. See also ref 5f,h,m.

(7) For a review of synthetic aspects of vitamin D, see: Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877−1952.

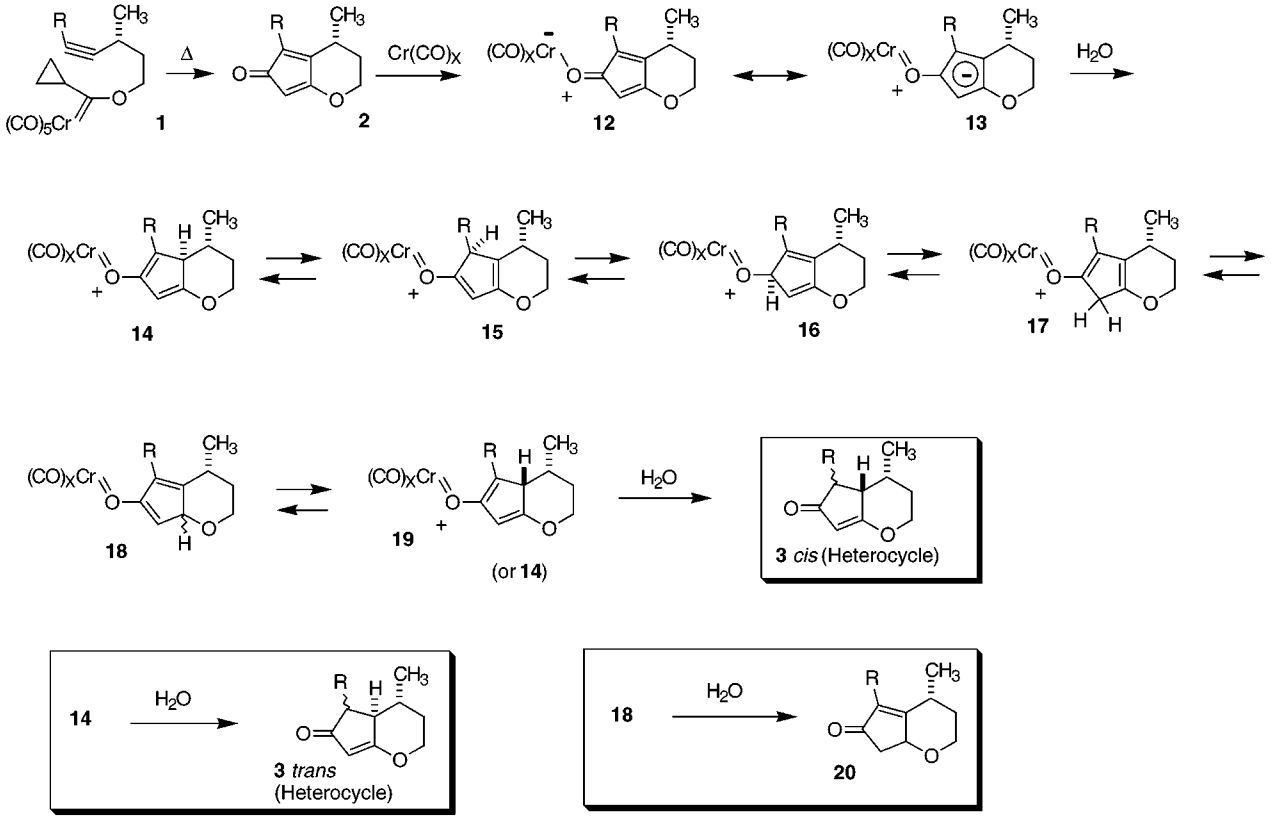
(8) For transformation of **5** into vitamin D_3, see ref 5m, followed by: (a) Kocienski, P. J.; Lythgoe, B.; Roberts, D. A. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 897−901. (b) Littlewood, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc. C* **1971**, 2955−2959. (c) Dawson, T. M.; Dixon, J.; Littlewood, P. S.; Lythgoe, B.; Saksena, A. K. *J. Chem. Soc. C* **1971**, 2960−2966. (d) Kocienski, P. J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1400−1404. (e) Kocienski, P. J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1405−1406.

(9) For a review of the biological activity of vitamin D and its synthetic analogues, see: Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocrine Rev.* **1995**, *16*, 200−257.

(10) (a) Wulff, W. D.; McCallum, J. S.; Kunng, F.-A. *J. Am. Chem. Soc.* **1988**, *110*, 7419−7434. (b) Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Speiss, E. J.; Wulff, W. D.; Zask, A. *Tetrahedron* **1985**, *41*, 5803−5812.

(11) The first stereochemical label refers to the stereochemistry of heterocyclic ring substituents, and the second label refers to the stereochemistry of carbocyclic ring substituents.

Scheme 5



and α-carbonyl hydrogens (3.2 and 3.4 Hz in **3B**-*trans-trans* and **3C**-*trans-trans*, respectively) compared with a larger value for the same couplings in isomers assigned as cis carbocycles (7.0 and 6.6 Hz in **3B**-*trans-cis* and **3C**-*trans-cis*, respectively); a similar correlation has been noted in similar systems.[2a,12] The stereochemistry of the remaining isomers was assigned on the basis of the observation that the diastereotopic hydrogens of the methylene group next to oxygen are separated by about 0.2 ppm in the trans heterocycles, while these same hydrogens appear as one signal in the cis heterocycles.

Rationale for the Stereoselectivity. As noted in previous studies, the substituents on the carbocyclic ring undergo isomerization under the conditions of carbene−alkyne coupling, and the trans carbocycle is usually the major product of the reaction;[2a,12] this equilibration occurs predominantly at the α-carbonyl position on the basis of deuterium−exchange studies.[12] The major heterocyclic ring stereoisomer from the intramolecular alkyne−carbene coupling reaction also corresponds to the thermodynamically more stable isomer. The stereochemistry, which arises during the cyclopentadienone reduction step, can be rationalized on the basis of the series of events depicted in Scheme 5. First, the cyclopentadienone oxygen complexes to chromium (**12**),[13] and negative charge is delocalized into the five-membered ring through back-bonding (**13**).[14] The anionic cyclopentadiene ring is then protonated once to afford cyclopentadiene derivative **14**, which then undergoes a series of 1,5-hydrogen shifts,[15] ultimately equilibrating cyclopentadienide stereoisomers **14** and **19**. Protonation of stereoisomers **14** or **19** a second time affords the observed major isomer, **3**-*trans* or **3**-*cis*. This sequence of events is supported by several previous observations:[12] The high degree of anionic character of the five-membered ring is supported by the appearance of β-elimination products when propargyl ethers couple with cyclopropylcarbene complexes. The hydride shifts are supported by the scrambling of the deuterium label when D_2O is used as the proton source. That cyclopentadiene regioisomers **14** and **19** are the major species at equilibrium is supported by the exclusive formation of vinylogous ester regioisomers and not 4-alkoxy-2-cyclopentenone derivatives (e.g., **20**) or unconjugated cyclopentenones, and previous studies have shown that vinylogous ester isomers (e.g., **3**) and cyclopentenones analogous to **20** do not interconvert under the conditions required for the alkyne−cyclopropylcarbene coupling, although isomerization to vinylogous ester derivatives can be effected by treatment with base.

An alternative but more direct explanation for the stereochemistry would involve preferential protonation of intermediate **13** from the pseudoaxial direction[16] giving

(12) Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394−8404.

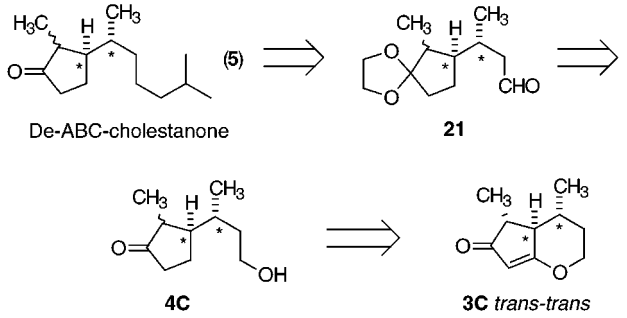
(13) Both oxygen and η^4-diene complexes have been proposed in the reaction of cyclopentadienones with group VI metal carbonyls. These results are more consistent with a simple reduction−protonation sequence, which employs an oxygen-bound complex. (a) Brown, D. A.; Hargaden, J. P.; McMullin, C. M.; Gogan, N.; Sloan, H. *J. Chem. Soc.* **1963**, 4914−4918. (b) Adams, H.; Bailey, N. A.; Hempstead, P. D.; Morris, M. J.; Riley, S.; Beddoes, R. L.; Cook, E. S. *J. Chem. Soc., Dalton Trans.* **1993**, 91−100.

(14) Cyclopentadienones are excellent electron acceptors. (a) Östrich, S.; Broser, W.; Kurreck, H. Z. *Naturforsch. B* **1977**, *32B*, 686−692. (b) Burk, M. J.; Calabrese, J. C.; Davidson, F.; Harlow, R. L.; Roe, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 2209−2222.

(15) This process is anticipated to be very rapid at the reaction temperature. For a recent example, see: Himeda, Y.; Yamataka, H.; Ueda, I.; Hatanaka, M. *J. Org. Chem.* **1997**, *62*, 6529−6538.

(16) (a) Caine, D. *Org. React.* **1976**, *23*, 1−258. (b) House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2800−2810.

Scheme 6



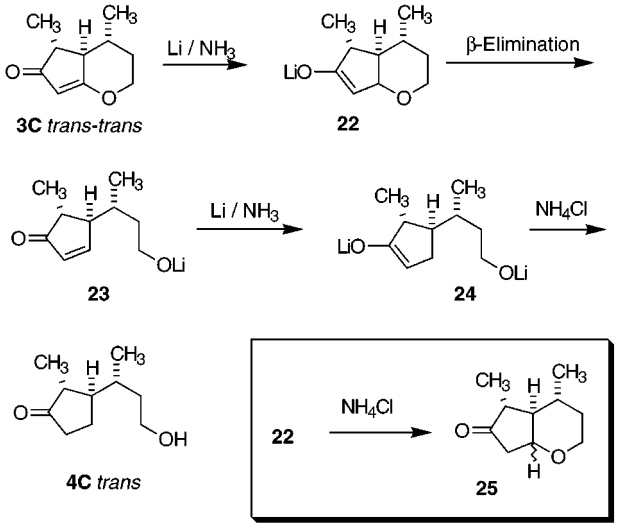
cyclopentadiene **14**, followed by a second protonation to afford cyclopentenone **3** *trans*. This scenario is, however, not consistent with previous studies of reactions conducted in the presence of D_2O, where the deuterium incorporation at the 2-, 4-, and 5-positions (cyclopentenone numbering) was noted.[12]

Cyclopentenone 3C-*trans-trans* as an Intermediate for Vitamin D Synthesis. As noted in Table 1, the intramolecular alkyne−cyclopropylcarbene coupling reaction offers a very effective method to control the relative configuration between the asterisked carbons in the major isomer of **3C** (Scheme 6).[5] This stereochemistry matches that present in numerous steroid derivatives such as vitamin D_3. The retrosynthetic analysis for a formal total synthesis of vitamin D_3 is depicted in Scheme 6. The objective in this manuscript is to transform cyclopentenone **3C**-*trans-trans* into de-ABC-cholestan-14-one (**5**), which has previously been converted to vitamin D_3.[8] The synthesis requires the reductive ring opening of the vinylogous ester functionality in **3C**-*trans-trans*, followed by a chain extension of the resulting alcohol **4C**.

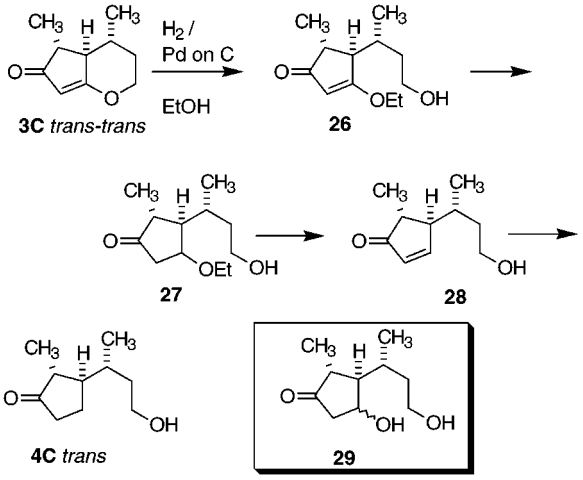
The synthesis of de-ABC-cholestan-14-one in this paper employs the purified major isomer, **3C**-*trans-trans*. Since the enolate of de-ABC-cholestan-14-one was employed for further transformation to vitamin D_3,[5m,7] either **3C**-*trans-trans* or **3C**-*trans-cis* could in theory be employed for the synthesis of vitamin D_3. Thus, the stereoselectivity of the alkyne−carbene thermolysis reaction can be regarded as 95:5 since **3C**-*trans-trans* (90% of the mixture) and the *trans-cis* isomer (5% of the mixture) both have the correct relative stereochemistry at the asterisked carbons, while the other minor isomer, **3C** *cis-trans* (5% of the mixture), has the wrong relative stereochemistry.

Reductive Ring Opening of Vinylogous Esters. A transformation similar to the desired reductive ring opening has been reported for 3-ethoxycyclohexenone using a dissolving metal reduction at −33 °C, followed by protonation.[4] Exposure of cyclopentenone **3C**-*trans-trans* to these conditions afforded only the net hydrogenation product **25** in 84% yield (Scheme 7). Apparently, the critical β-elimination step (**22** → **23**) does not occur at −33 °C. Dissolving metal reduction at 25 °C in ethylenediamine afforded a mixture of the desired reductive ring opening product **4C**-*trans* (46%) and hydrogenation product **25** (40%). The desired transformation was most successfully accomplished by catalytic hydrogenation in ethanol (Scheme 8). In this reaction, the desired reductive ring opening product was the major product (65%), accompanied by a side product tentatively identified as β-hydroxy ketone derivative **29** (17%); the spectral data for **29** are also consistent with the compound where

Scheme 7



Scheme 8



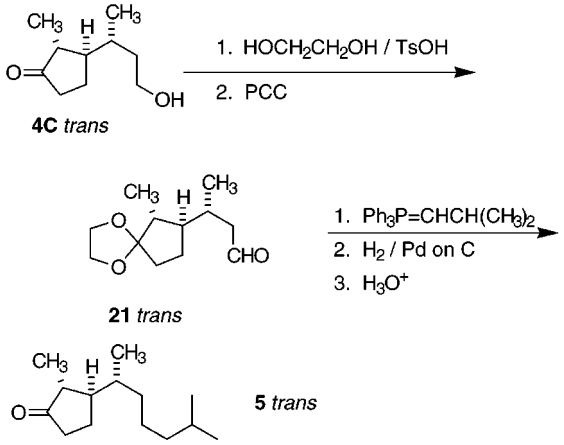
the position of the C=O and OH groups are reversed. On the basis of previous observations,[2b] the conversion of **3C** *trans-trans* to **4C**-*trans* is postulated to occur via palladium-catalyzed ether exchange, affording ethoxycyclopentenone **26**, followed by hydrogenation and β-elimination. Compounds similar to **26** have previously been noted in the catalytic hydrogenation of vinylogous esters in ethanol solvent, while simple hydrogenation products (e.g., **25**) are the major products from hydrogenation in THF. The origin of the β-hydroxycarbonyl compound is unclear.

Eventual transformation of keto alcohol **4C**-*trans* into de-ABC-cholestan-14-one is relatively straightforward and is depicted in Scheme 9. Protection of the ketone, followed by oxidation of the alcohol to an aldehyde, followed by chain extension and deprotection affords de-ABC-cholestan-14-one. The overall process occurs without epimerization of any of the stereogenic centers. The overall conversion of **4C**-*trans* to de-[ABC]-cholestan-14-one occurs in 88% yield.

Conclusion

The intramolecular coupling of alkyne−cyclopropylcarbene chromium complexes featuring a propargylic stereocenter proceeds with a high degree of stereoselectivity and leads to cyclopentenones fused to tetrahydro-

Scheme 9



pyran rings. The reaction produces preferentially the trans heterocycle, and this selectivity has been attributed to thermodynamic control during the reduction of a cyclopentadienone intermediate. The major diastereomer produced in this coupling reaction matches the stereochemical features found in steroid derivatives, and this reaction has been used as the cornerstone for a stereoselective formal total synthesis of vitamin D_3 through the cyclopentanone derivative de-ABC-cholestan-14-one (**5**). Subsequent reductive ring opening of the major isomer using catalytic hydrogenation followed by a chain extension provides (±)-de-ABC-cholestan-14-one in stereochemically pure form. Further evaluation of the scope and limitation of the stereoselective five-membered ring-forming reaction is presently underway in our laboratory.

Experimental Section

General methods have been described previously.[12]

General Procedure I: Conversion of Alkynols to Carbene Complexes. To the solution of acylate salt **11**[17] (400 mg, 1.20 mmol) in 20 mL of dichloromethane at 0 °C under nitrogen was added acetyl chloride (0.08 mL, 1.20 mmol) via syringe, followed by immediate addition of the alkynol (1.20 mmol). The reaction mixture was stirred at 0 °C for about 1 h and then warmed to 25 °C and stirred for 20 min. The solvent was removed on a rotary evaporator. Flash chromatography (hexane eluent) of the residue gave the pure carbene complex after solvent removal.

Preparation of Alkyne−Carbene Complex 1C. General procedure I was followed using a solution of 3-methyl-4-hexyn-1-ol[18] (350 mg, 3.13 mmol) in dichloromethane (20 mL), acylate salt **11**[17] (1050 mg, 3.13 mmol), and acetyl chloride (0.22 mL, 1.7 mmol) in dichloromethane (20 mL). After chromatographic purification, a yellow oil (790 mg, 71%) identified as carbene complex **1C** was obtained: ^{1}H NMR ($CDC1_3$) δ 5.03 (t, 2 H, J = 5.6 Hz), 3.45 (m, 1 H), 2.29 (m, 1 H), 1.94 (m, 2 H), 1.75 (d, 3 H, J = 2.3 Hz), 1.24 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 351.6, 223.7, 216.8, 81.2, 78.9, 77.7, 41.3, 36.4, 23.2, 21.5, 17.6, 3.3; IR (CCl_4) 2060 (s), 1921 (vs) cm^{-1}; MS (CI) *m/e* 356 (M, 3), 164 (100); HRMS calcd for $C_{16}H_{16}CrO_6$ 356.0352, found 356.0339

General Procedure II: Thermolysis of Alkyne−Carbene Complexes. To a three-neck round-bottom flask equipped with a reflux condenser and rubber septum, under nitrogen, were added toluene (100 mL) and water (1 mL), and the solution was heated to reflux. To this refluxing solution was added a solution of carbene complex in toluene (30 mL) via syringe pump over a period of 4 h. After the addition was complete, the mixture was heated at reflux for an additional 20 h and then cooled to room temperature. The resulting green mixture was filtered through Celite, and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel.

Thermolysis of Alkyne−Carbene Complex 1C. General procedure II was followed using carbene complex **1C** (465 mg, 1.31 mmol). Purification by flash chromatography on silica gel using hexane/ethyl acetate (3:2) as the eluent provided two fractions.

The first fraction was identified as compound **3C**-*trans-trans* (137 mg, 63%): ^{1}H NMR ($CDCl_3$) δ 5.20 (d, 1 H, J = 1.6 Hz), 4.30 (ddd, 1 H, J = 11.1, 5.8, 4.6 Hz), 4.05 (ddd, 1 H, J = 11.1, 8.3, 4.5 Hz), 2.09 (qd, 1 H, J = 7.3 (q), 3.4 (d) Hz), 1.99 (ddd, 1 H, J = 11.1, 3.4, 1.6 Hz), 1.91 (dddd, 1 H, J = 14.0, 5.8, 5.8, 4.5 Hz), 1.59 (m, 2 H), 1.15 (d, 3 H, J = 7.3 Hz) 1.06 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 206.3, 189.1, 106.2, 68.7, 51.1, 46.4, 32.3, 31.7, 20.6, 15.7; IR (neat) 1694 (s), 1614 (s) cm^{-1}; MS (EI) *m/e* 166 (M, 91), 151 (73) 111 (100); HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0994.

The second fraction was a mixture of two compounds, believed to a mixture of compounds **3C**-*trans-cis* and **3C**-*cis−trans* (15.2 mg, 7%). Further purification using preparative thin-layer chromatography afforded a small sample of pure **3C**-*trans-cis*: ^{1}H NMR ($CDCl_3$) δ 5.27 (d, 1 H, J = 1.9 Hz), 4.39 (dt, 1 H, J = 11.2 (d), 4.5 (t) Hz), 4.06 (td, 1 H, J = 11.2 (t), 3.6 (d) Hz), 2.61 (qd, 1 H, J = 7.2 (q), 6.6 (d) Hz), 2.53 (ddd, 1 H, J = 11.2, 6.6, 1.9 Hz), 1.94 (m, 1 H), 1.80 (m, 1 H), 1.60 (m, 1 H), 1.15 (d, 3 H, J = 6.9 Hz), 1.07 (d, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 208.5, 189.1, 105.8, 68.9, 46.8, 43.2, 32.0, 26.5, 21.2, 14.0; IR (neat) 1682 (s, 1595 (s) cm^{-1}; MS (EI) *m/e* 166 (100), 151 (87), 111 (96); HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0992. The following resonances appear in the mixture but not in purified **3C**-*trans-cis* and have been attributed to **3C**-*cis−trans*: ^{1}H NMR ($CDCl_3$) δ 5.28 (d, 1 H, J = 1.4 Hz), 4.28 (t, 2 H, J = 6.3 Hz), 1.13 (d, 3 H, J = 6.5 Hz), 0.93 (d, 3 H, J = 7.0 Hz).

The ratio of 90:5:5 was determined by NMR integration on the alkene protons at around 5.2 ppm prior to attempted isomer separation.

Reductive Ring Opening of Vinylogous Ester Derivative 3C-*trans-trans* Using Catalytic Hydrogenation. To a 250 mL round-bottom flask equipped with a three-way adapter and a stir bar was added a solution of vinylogous ester **3C**-*trans-trans* (205 mg, 1.24 mmol) in ethanol (200 mL) followed 10% palladium on carbon (10 mg). The reaction system was evacuated and refilled with nitrogen (three times) followed by hydrogen (three times); an aspirator was used as the vacuum source. The hydrogen pressure was adjusted to about 1 atm using a balloon. The reaction mixture was allowed to stir at room temperature under a hydrogen atmosphere for a 12 h period. The catalyst was removed by filtration through Celite, and the solvent was removed on a rotary evaporator. Purification of the residue by

(17) Herndon, J. W.; Tumer, S. U.; McMullen, L. A.; Matasi, J. J.; Schnatter, W. F. K. In *Advances in Metal−Organic Chemistry;* Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1994; Vol. III, pp 51−95.

(18) See the Supporting Information.

preparative TLC using hexane/ethyl acetate (3:2) as the eluent led to two major fractions.

The compound in the first fraction was assigned as reductive ring opening product **4C**-*trans* (135 mg, 65%): ^{1}H NMR ($CDCl_3$) δ 3.75 (ddd, 1 H, J = 10.4, 7.8, 5.0 Hz), 3.64 (ddd, 1 H, J = 10.4, 7.3, 7.3 Hz), 2.32 (ddt, 1 H, J = 18.2, 8.7, 1.2(t) Hz), 2.09 (ddd, 1 H, J = 18.2, 11.6, 9.0 Hz), 1.98 (m, 1 H), 1.88 (m, 1 H), 1.69 (m, 3 H), 1.48 (ddd, 1 H, J = 23.2, 11.4, 8.2 Hz), 1.34 (m, 1 H), 1.07 (d, 3 H, J = 6.9 Hz), 0.99 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 221.4, 61.2, 50.3, 46.9, 37.2, 35.3, 31.2, 23.3, 17.7, 14.0; IR (neat) 3408 (s), 1732 (s) cm^{-1}; MS (EI) *m/e* 170 (M, 1), 97 (100); HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1293.

The compound in the second fraction was assigned as keto diol **29** (39.3 mg, 17%; appears to be a 9:1 mixture of stereoisomers): ^{1}H NMR ($CDCl_3$) δ 4.19 (ddd, 1 H, J = 5.5, 4.0, 1.5 Hz), 3.67 (m, 2 H), 2.39 (m, 1 H), 2.30 (br s, 1 H), 2.27 (d, 1 H, J = 4.0 Hz) 2.05 (m, 1 H), 1.95 (m, 1 H), 1.20 (m, 1 H), 1.19 (d, 3 H, J = 7.4 Hz), 1.04 (d, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 219.0, 70.6, 62.1, 49.7, 45.6, 43.4, 26.2, 25.3, 18.8, 12.8; IR (neat) 3400 (s), 1735 (s) cm^{-1}; MS (EI) *m/e* 186 (M, 1), 125 (100); HRMS calcd for $C_{10}H_{18}O_3$ 186.1256, found 186.1238.

Conversion of Keto Alcohol 4C-*trans* to the Corresponding Ketal. To a 100 mL round-bottom flask equipped with a Dean-Stark trap and a condenser was added a solution of keto alcohol **4C**-*trans* (75.6 mg, 0.45 mmol) in ethylene glycol (559 mg, 9.00 mmol) and *p*-toluenesulfonic acid monohydrate (30 mg 0.16 mmol) in dry benzene (50 mL) at room temperature. The reaction mixture was refluxed for 8 h and then was cooled to room temperature. Saturated aqueous sodium bicarbonate solution (30 mL) was added, and the mixture was poured into water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with water (50 mL) and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator. Purification of the residue by preparative TLC using hexane/ethyl acetate (3:2) as the eluent afforded the ketal (85.6 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 3.88 (m, 4 H), 3.73 (m, 1 H), 3.62 (ddd, 1 H, J = 10.2, 7.4, 7.4 Hz), 1.80−1.60 (m, 4 H), 1.50 (m, 1 H), 1.30 (m, 3 H), 0.91 (d, 3 H, J = 6.6 Hz), 0.89 (d, 3 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 118.3, 64.7, 64.4, 61.6, 49.9, 43.2, 35.7, 34.7, 32.0, 24.2, 18.0, 13.9; IR (neat) 3418 (s) cm^{-1}; MS (EI) *m/e* 214 (M, 1), 99 (100); HRMS calcd for $C_{12}H_{20}O_3$ 214.1569, found 214.1576.

Synthesis of Ketal Aldehyde 21-*trans*. To a solution of the ketal alcohol from the previous experiment (89.5 mg, 0.42 mmol) in dichloromethane (20 mL) was added pyridinium chlorochromate (108 mg, 0.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for a 2 h period. The reaction mixture was quenched with water (30 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed on a rotary evaporator. Purification of the residue by preparative TLC using hexane/ethyl acetate (3:2) as the eluent yielded aldehyde **21**-*trans* (85.6 mg, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.75 (dd, 1 H, J = 2.6, 1.4), 3.88 (m, 4 H), 2.45 (m, 1 H), 2.15 (m, 2 H), 1.58 (m, 5 H), 1.27 (m, 2 H), 0.96 (d, 3 H, J = 6.3 Hz), 0.92 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 202.9, 118.0, 64.7, 64.4, 49.5, 49.3, 47.3, 43.5, 34.6, 32.5, 30.4, 24.3, 18.7, 14.0; IR (neat) 1726 cm^{-1}; MS (EI) *m/e* 212 (M, 1), 141 (39), 99 (100); HRMS calcd for $C_{12}H_{18}O_3$ 212.1413, found 212.1422.

Synthesis of De-ABC-cholestan-14-one Ketal. To a solution of (isobutyl)triphenylphosphonium bromide (72 mg, 0.18 mmol) in diethyl ether (20 mL) was added *n*-butyllithium (0.11 mL of a 1.6 M hexane solution, 0.18 mmol) at −78 °C. The reaction was stirred at −78 °C for 0.5 h. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The reaction mixture was cooled to 0 °C, and then a solution of ketal aldehyde **21**-*trans* (38 mg, 0.18 mmol) in diethyl ether (10 mL) was added at −78 °C. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with water (30 mL) and extracted with diethyl ether (3 × 50 mL). The organic phases were dried over anhydrous magnesium sulfate, and the solvent was removed on a rotary evaporator. The residue was dissolved in dry hexane (50 mL), the solid portion was removed by filtration, and the solvent was removed on a rotary evaporator to give a light yellow color oil. The compound was not further purified but immediately subjected to hydrogenation. To a 250 mL round-bottom flask equipped with a three-way adapter and a stir bar was added a solution of the light yellow compound and 10% palladium−carbon (10 mg) in ethanol (50 mL) at room temperature. The reaction system was evacuated and refilled with nitrogen (three times) followed by hydrogen (three times); an aspirator was used as the vacuum source. The hydrogen pressure was adjusted to about 1 atm using a balloon. The reaction mixture was stirred at room temperature for 12 h. The catalyst was removed by filtration through Celite, and the solvent was removed on a rotary evaporator. Purification of the residue by preparative TLC using hexane/ethyl acetate (3:2) as the eluent led to de-ABC-cholestan-14-one ketal (40.5 mg, 90%): ^{1}H NMR ($CDCl_3$) δ 3.87 (m, 4 H), 1.78 (m, 1 H), 1.70 (m, 3 H), 1.46 (m, 3 H), 1.31 (m, 3 H), 1.12 (m, 3 H), 0.98 (m, 1 H), 0.88 (d, 3 H, J = 7.0 Hz), 0.86 (d, 3 H, J = 6.4 Hz), 0.831 (d, 3 H, J = 6.6 Hz), 0.828 (d, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 118.4, 64.6, 64.4, 50.0, 43.1, 39.3, 35.5, 34.8, 32.7, 27.9, 25.2, 24.4, 22.7, 22.5, 17.9, 14.0; MS (EI) *m/e* 254 (M, 0.2), 99 (100); HRMS calcd for $C_{16}H_{30}O_2$ 254.2246, found 254.2240.

Synthesis of De-ABC-cholestan-14-one (5). To a solution of de-ABC-cholestan-14-one ketal (39.6 mg, 0.16 mmol) in acetone (20 mL) was added 10% hydrochloric acid (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with water (30 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, and the solvent was removed on a rotary evaporator. Purification of the residue by preparative TLC using hexane/ethyl acetate (3:2) as the eluent led to de-ABC-cholestan-14-one (**5**) (31.9 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 2.23 (m, 1 H), 2.06 (m, 1 H), 1.91 (m, 2 H), 1.59 (m, 2 H), 1.44 (m, 2 H), 1.33 (m, 2 H), 1.15 (m, 4 H), 1.06 (d, 3 H, J = 6.9 Hz), 0.95 (d, 3 H, J = 6.7 Hz), 0.85 (d, 3 H, J = 6.6 Hz), 0.84 (d, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 221.8, 50.3, 46.9, 39.2, 37.3, 34.7, 32.6, 27.9, 25.2, 23.3, 22.7, 22.5, 17.8, 14.1; IR (neat) 1744 (s) cm^{-1}; MS (El) *m/e* 210 (m, 8), 140 (3), 126 (5), 125 (10), 99 (2), 98 (11), 97 (100), 84 (16), 83 (13), 71 (14), 69 (30); HRMS calcd for $C_{14}H_{26}O$ 210.1984, found 210.1986.

Literature-reported ^{13}C NMR data of compound **5**:

Ficini's results:[19] ^{13}C NMR ($CDCl_3$) δ 221.4, 50.3, 46.9, 39.3, 37.3, 34.8, 32.7, 27.9, 25.3, 23.4, 22.7, 22.5, 17.7, 14.1.

Tokoroyama's results:[6] ^{13}C NMR ($CDCl_3$) δ 221.71, 50.34, 46.95, 39.29, 37.35, 34.81, 32.68, 27.98, 25.26, 23.41, 22.77, 22.50, 17.80, 14.14.

Takano's results:[5h] ^{13}C NMR ($CDCl_3$) δ 221.4, 50.3, 46.9, 39.3, 37.3, 34.8, 32.6, 28.0, 25.2, 23.4, 22.8, 22.5, 17.8, 14.1.

(19) Desmaele, D.; Ficini, J.; Guingant, A.; Kahn, P. *Tetrahedron Lett.* **1983**, *24*, 3079−3082.

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Supporting Information Available: Synthetic procedures for synthesis of alkynols, synthesis and thermolysis of complexes **1A** and **1B**, and dissolving metal reductions. Photocopies of ^{1}H and ^{13}C NMR spectra for compounds produced in these studies have also been included (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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