noteworthy because of the considerable potential for proton transfer from one ester α-CH unit to the various ester enolate intermediates in this process. This easy, one-pot, 2 + 2 + 2, Michael–Michael–Ring–Closure (MIMIRC) process,[4] involving a terminating Dieckmann cyclization[6] with overall formation of three carbon–carbon bonds (**2a–c**), represents a simple, convenient, and potentially versatile synthetic method for joining three 2-carbon components into 6-membered carbocycles of varied substitution pattern.[4e]

The generality of this synthetic method is illustrated in Scheme I. For example, methyl phenylthioacetate reacted with lithium diisopropylamide (LDA) in THF at −78 °C and then with 2.2 equiv of methyl acrylate to form, after acidic workup, trisubstituted cyclohexanone **3** on a multigram scale as a mixture of stereoisomers in 72% yield (Scheme II). Lower yields of dimethyl ester cycloadduct **3** were obtained when the ester group of the initiator was different from the ester group of the acrylate; lithium alkoxides formed in the terminal Dieckmann cyclization caused transesterifications. Stereoisomeric β-keto esters **3** were decarboxylated (NaCl, DMSO, 150 °C, 4.5 h)[7] to form stereochemically homogeneous, polyfunctional ketone **4** in overall 57% yield based on starting methyl phenylthioacetate. Alternatively, stereoisomeric α-thio ketones **3** were oxidized into the corresponding sulfoxides (MCPBA, 0 → 25 °C, 1 h);[8] pyrolysis (refluxing benzene)[9] produced a conjugated cyclohexenone having substantial dienol character. Dehydrogenation (DDQ, refluxing benzene)[10] formed regiospecifically trisubstituted benzene **5** in overall 42% yield based on starting methyl phenylthioacetate.

Spirobicyclic compounds, often useful synthons[11] and characteristic of different families of biologically active natural products,[12] in general are not easily prepared directly from simple components. As shown in Scheme I, lithium enolates of several carbocyclic and heterocyclic carboxylate esters reacted cleanly with 2 equiv of an acrylate ester to form spirobicyclic adducts **6** in 45–64% yields. This one-pot, three-component coupling process represents interrupted polymerizations leading easily and directly to regiospecifically polyfunctionalized spirobicyclic adducts.

In summary, the results reported here demonstrate (1) that lithio acetates, in which the α-carbon atom is either unsubstituted or mono- or disubstituted, initiate polymerization of acrylate esters; (2) that in THF at −78 °C such polymerization is effectively interrupted by a terminating Dieckmann cyclization; and (3) that this three-component coupling process leads rapidly and conveniently on a multigram scale to regiospecifically tri- and tetrasubstituted 6-membered carbocycles including spirobicyclic adducts. We are continuing to explore the scope and applications of these interrupted polymerizations.

Acknowledgment. We thank the donors of Petroleum Research Fund, administered by the American Chemical Society, and the NSF (Grant CHE-86-07974) for financial support and T. Kishimoto and C. Oh of this department for some fine experimental help.

Supplementary Material Available: A complete experimental section including descriptive procedures and full characterization data (6 pages). Ordering information is given on any current masthead page.

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Efficient Enantiospecific Synthesis of Key A-Ring Synthons for the Preparation of 1α,25-Dihydroxyvitamin D_3 Using a Chromium(II)-Mediated Reaction

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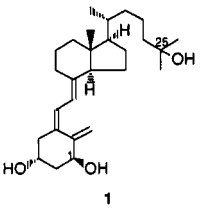
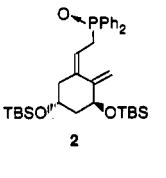
Summary: Key A-ring synthons for the synthesis of 1α,25-dihydroxyvitamin D_3 have been prepared efficiently from (*R*)-(−)-carvone by use of diastereoselective chromium(II)-mediated addition of an allylic halide to an aldehyde as a key step.

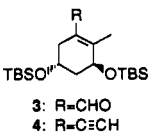
Sir: Of the known vitamin D_3 metabolites, 1α,25-dihydroxyvitamin D_3 (**1**), is considered to be the most potent stimulator of calcitropic effects such as intestinal calcium absorption and bone calcium mobilization.[1] Recently, this hormone has also been found to suppress proliferation and induce differentiation in human myeloid leukemia cells.[2] These potent biological activities therefore have stimulated efforts toward the synthesis of 1α,25-dihydroxyvitamin D_3 (**1**).[2-4]



1



2



3: R=CHO
4: R=C≡CH

TBS=^{t}BuMe$_2$Si–

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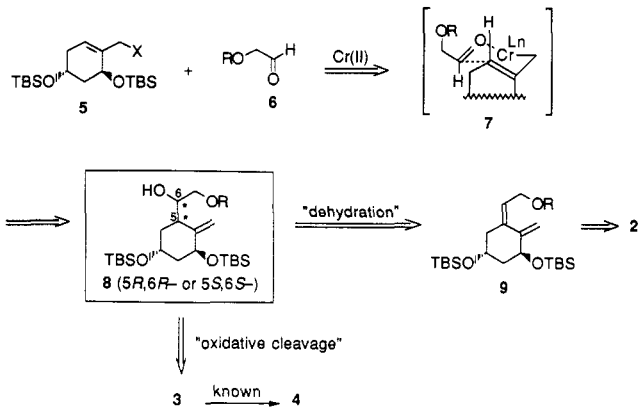
0022-3263/89/1954-3515$01.50/0

Scheme I

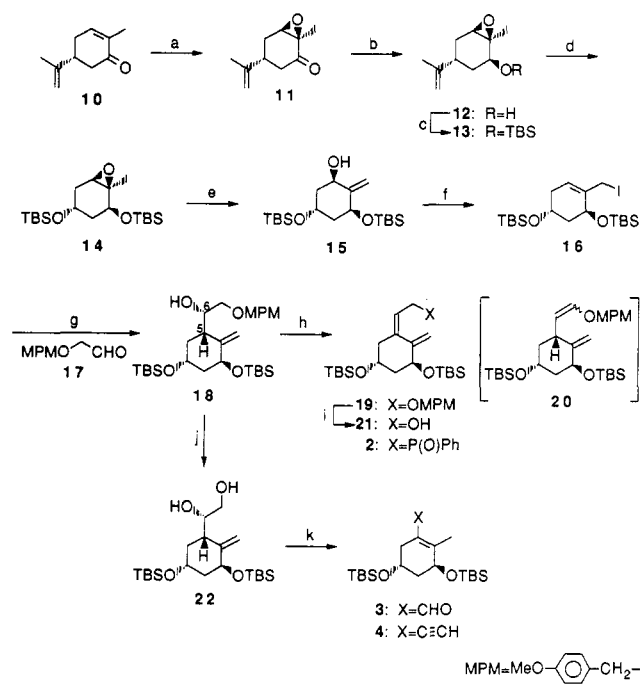


On the basis of Lythgoe's methodology[3a] devised to synthesize the calciferols via convergent routes, three compounds, **2**,[4b] **3**,[4a,d,5] and **4**,[4f,g] have so far been prepared as A-ring synthons, and each of them has functioned effectively in the synthesis of 1α,25-dihydroxyvitamin D_3 (**1**). Most of the recent syntheses[4b,d-g] of these A-ring synthons utilized (*S*)-(+)-carvone as chiral starting material, except the synthesis[4a] of **3** from (−)-quinic acid. However, use[6] of (*R*)-(−)-carvone (**10**) remains unexploited despite the obvious cost advantage over its enantiomer. We now wish to report efficient enantiospecific syntheses of the A-ring synthons **2**, **3**, and **4** starting with (*R*)-(−)-carvone (**10**).

Our basic strategy is outlined in Scheme I. We envisaged formation of a common precursor (**8**) from allylic halide **5** and aldehyde **6** by taking advantage of the chromium(II)-mediated reaction developed by Hiyama and Nozaki et al.[7] We anticipated that the crucial construction of the conjugated diene of **2** would be achieved by stereo- and regioselective dehydration of **8** through a "trans elimination" process provided the chromium(II)-mediated reaction proceeded with a high degree of threo selectivity via six-center transition state **7** as reported.[8]

The known epoxide **11**,[9] easily obtained by epoxidation of (*R*)-(−)-carvone (**10**) with alkaline hydrogen peroxide, was stereoselectively reduced with lithium tri-*sec*-butylborohydride[10] to give a 13:1 mixture[11] of alcohol **12**,[12] $[\alpha]^{28}_D$ −51.6° (*c* 1.07, $CHCl_3$), and its epimer.[13] After silylation of **12** to **13**, $[\alpha]^{28}_D$ −31.1° (*c* 1.03, $CHCl_3$), oxidative degradation of the isopropenyl group to the hydroxyl group was carried out by the established procedure involving Criegee rearrangement of the methoxy peroxyester.[4d,f,15] Thus, upon sequential ozonolysis, Criegee rearrangement, methanolysis, and protection of the resulting hydroxyl group as its *tert*-butyldimethylsilyl ether **13** yielded epoxide **14**, $[\alpha]^{24}_D$ −21.1° (*c* 1.26, $CHCl_3$). It is worthy of note that, in this particular case, ozonolysis of **13** without sodium bicarbonate as an acid scavenger resulted in decomposition of the α-methoxy hydroperoxide due to acidic impurities in the ozone. Treatment of **14** with diethylaluminum 2,2,6,6-tetramethylpiperidide[16] led to regioselective formation of allyl alcohol **15**, $[\alpha]^{22}_D$ −5.8° (*c* 1.07, $CHCl_3$), which was then converted to iodide **16**, $[\alpha]^{23}_D$ −12.4° (*c* 0.92, $CHCl_3$), via the corresponding mesylate. The crucial chromium(II)-mediated reaction of iodide **16** with aldehyde **17** proceeded with excellent diastereoselectivity to afford alcohol **18**,[17] $[\alpha]^{27}_D$ +7.9° (*c* 1.11, $CHCl_3$),

Scheme II[a]



[a] (a) H_2O_2, NaOH, MeOH, 90%; (b) L-Selectride, THF, −65 °C, 96% (**12**:epimer = 13:1); (c) *t*-BuMe_2SiCl, imidazole, DMF, 98%; (d) (i) O_3, $NaHCO_3$, CH_2Cl_2–MeOH (5:1 v/v), −68 °C, (ii) Ac_2O, Et_3N, DMAP (catalyst), CH_2Cl_2, reflux, (iii) K_2CO_3, MeOH, (iv) as in c, 66% overall; (e) DATMP, benzene, 0 °C, 96%; (f) (i) MsCl, DMAP, CH_2Cl_2, (ii) NaI, acetone, reflux, 93% overall; (g) 3 equiv of **17**, 6 equiv of $CrCl_3$, 3 equiv of LAH, THF, 97%; (h) 6 equiv of DEAD, 9 equiv of Ph_3P, THF, 87% (**19**:**20** = 6:1); (i) DDQ, 5% aq CH_2Cl_2, 91%; (j) (i) as in i, (ii) K_2CO_3, MeOH; (k) (i) $NaIO_4$, 30% aq THF, (ii) DBU, CH_2Cl_2, 79% overall from **18**.

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(4) (a) Desmaele, D.; Tanier, S. *Tetrahedron Lett.* **1985**, *26*, 4941. (b) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovič, M. R. *J. Org. Chem.* **1986**, *51*, 3098 and references therein. (c) Andrews, D. R.; Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819 and references therein. (d) Baggiolini, E. G.; Hennessy, B. M.; Iacobelli, J. A.; Uskokovič, M. R. *Tetrahedron Lett.* **1987**, *28*, 2095. (e) Castedo, L.; Mascareñas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1987**, *28*, 2099. (f) Aurrecoechea, J. M.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 4947. (g) Castedo, L.; Mascareñas, J. L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1988**, *29*, 1203.

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(6) There has been only one example[4e] in which (*R*)-(−)-carvone was used for the synthesis of an A-ring synthon.

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(8) (a) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (b) Hiyama, T. *J. Synth. Org. Chem. Jpn.* **1981**, *39*, 81. (c) Takai, K.; Utimoto, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 66.

(9) Klein, E.; Ohloff, G. *Tetrahedron* **1963**, *19*, 1091.

(10) This stereoselective reduction of **11** with lithium tri-*sec*-butylborohydride was developed in our laboratory independent of the work reported in a recent paper, see: Nishiyama, S.; Ikeda, Y.; Yoshida, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 105.

(11) Determined by 500-MHz ^1H NMR analysis.

(12) All new compounds isolated reported herein exhibited satisfactory ^1H NMR, IR, and mass spectra as well as combustion analytical data.

(13) It is interesting to note that reduction of **11** with $NaBH_4$–$CeCl_3$[14] at −20 °C in methanol proceeded with the opposite stereoselectivity giving the epimer of **12** as sole product in 90% yield.

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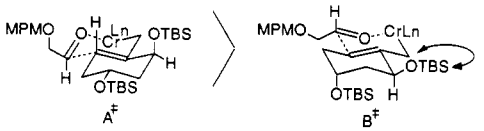
(15) Schreiber, S. L.; Liew, W. F. *Tetrahedron Lett.* **1983**, *24*, 2363.

(16) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513.

as the sole product in almost quantitative yield. One might rationalize the exclusive production of 18 by assuming a transition state resembling A‡ which is preferred over B‡ because of minimization of A[1,2] type of steric interactions.[19]



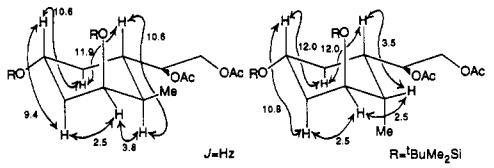
Having prepared the desired common intermediate 18, we then examined the stereo- and regioselective dehydration of 18 by several conventional methods in order to construct the requisite diene. However, unexpected difficulties were encountered in this transformation. For example, treatment of 18 with methanesulfonyl chloride in pyridine gave enol ether 20 as a major product instead of diene 19. These difficulties were eventually overcome by use of Mitsunobu's reagent.[20] Thus, reaction of alcohol 18 with triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran at room temperature gave the diene 19, $[\alpha]^{24}_D$ −9.6° (c 1.23, $CHCl_3$), and enol ether 20 in a ratio of 6:1. Oxidative deprotection[21] of 19 furnished dienol 21, mp 64–67 °C (lit.[4b] mp 69–71 °C), $[\alpha]^{25}_D$ +7.7° (c 0.73, EtOH) [lit.[4b] +7.9° (c 0.4, EtOH)], whose spectral data (^{1}H NMR, IR, MS) are identical with those reported.[4b] Since 21 has already been converted to phosphine oxide 2 in 82% yield by the Roche group,[4b] the present synthetic route should enable us to prepare 2 from (*R*)-(−)-carvone (10) in 25% overall yield (15 steps).

For the synthesis of A-ring synthons 3 and 4, alcohol 18 was converted to diol 22 by oxidative deprotection[21] followed by methanolysis of the resulting *p*-methoxybenzoates. Without purification, diol 22 was then successively subjected to oxidative cleavage and isomerization to furnish aldehyde 3, $[\alpha]^{29}_D$ −86.1° (c 0.32, EtOH) [lit.[4a] −91.1° (c 0.3, EtOH)], $[\alpha]^{28}_D$ −85.6° (c 1.08, $CHCl_3$) [lit.[4d] −86° (c 1.00, $CHCl_3$)], which exhibited spectral properties (^{1}H NMR, IR) in accord with those reported.[4a,d] Aldehyde 3 was thus obtained from (*R*)-(−)-carvone in 35% overall yield (14 steps). Since aldehyde 3 is a synthetic precursor of acetylene 4,[4f] the synthesis of 3 also means development of a new route to 4 from (*R*)-(−)-carvone (10).

Acknowledgment. We thank the Japan Society for the Promotion of Science for Japanese Junior Scientists for financial support (to Dr. Hirotoshi Numata).

Supplementary Material Available: Experimental procedures for preparation of 18, 19, 21, and 3 as well as spectral (^{1}H NMR, IR, MS) and analytical data for 12–16, 18, 19, 21, and 3 (4 pages). Ordering information is given on any current masthead page.

(17) The stereochemistry of 18 is tentatively assigned on the basis of mechanistic considerations in addition to the fact that dehydration of 18 gave the *Z* isomer 19 exclusively. Furthermore, on the basis of 500-MHz ^{1}H NMR spectral analysis of two diacetates derived from 18 (shown below) and MTPA ester derivatives of 18,[18] we empirically determined the configurations of C-5 and C-6 to be both *S*.



(18) Takano, S.; Takahashi, M.; Yanase, M.; Sekiguchi, Y.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1988**, 1827.
(19) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(20) Mitsunobu, O. *Synthesis* **1981**, 1.
(21) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

Nickel(0)-Promoted Cyclization of 1,*n*-Diynes with Isocyanide: The First Practical Synthesis of Polycyclic Iminocyclopentadienes

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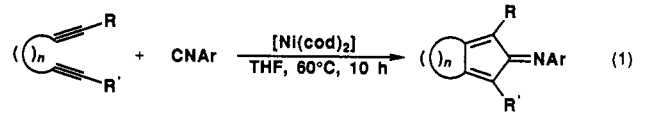
Received May 11, 1989

Summary: 1,*n*-Diynes having alkyl, aryl, and trimethylsilyl groups as the terminal substituents undergo cyclization with 2,6-dimethylphenyl isocyanide in the presence of a stoichiometric amount of bis(cyclooctadiene)nickel(0) to form polycyclic iminocyclopentadienes as red-orange crystals or oils, which show interesting spectral properties and chemical reactivities.

Sir: We have recently reported a one-step synthesis of polycyclic iminocyclopentenes via nickel(0)-promoted cyclization of enynes with isocyanides.[1] Reported herein is a similar cyclization of diynes[2] to form polycyclic iminocyclopentadienes,[3] nitrogen analogues of cyclopentadienones (eq 1).



Cyclopentadienones have long been studied from both of the synthetic and theoretical points of view, but the substituents on the ring have been restricted only to the stabilizing groups such as aryl and *tert*-butyl.[4] In 1980, Vollhardt and his co-workers reported a cobalt-mediated

(1) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286.
(2) Transition metal mediated cyclization of diynes have recently been studied extensively. (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (c) Nugent, W. A.; Thorn, D. L.; Harlow, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 2788. (d) Fagan, P. J.; Nugent, W. A. *J. Am. Chem. Soc.* **1988**, *110*, 2310. (e) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. (f) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. (g) Tsuda, T.; Morikawa, S.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 3140. (h) Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570. (i) Tamao, K.; Kobayashi, K.; Ito, Y., submitted for publication.
(3) Transition metal promoted cyclization of diphenylacetylene or analogues with isocyanides has been reported. (a) Co: Yamazaki, H.; Wakatsuki, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1239. (b) Rh: Mueller, E. *Synthesis* **1974**, 761. (c) Ni, Pd: Suzuki, Y.; Takizawa, T. *J. Chem. Soc., Chem. Commun.* **1972**, 837. (d) Ni: Eisch, J. J.; Aradi, A. A.; Han, K. I. *Tetrahedron Lett.* **1983**, *24*, 2073. Other iminocyclopentadiene chemistry: (e) Freeman, B. H.; Lloyd, D.; Singer, M. I. C. *Tetrahedron* **1972**, *28*, 343. (f) Atkinson, R. S.; Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2619.
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