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O-1-(1,3-BUTADIENYL) CARBAMATES AS DIELS-ALDER DIENES: STEREOSPECIFIC SYNTHESIS OF (±)-HERNANDULCIN AND CONGENERS

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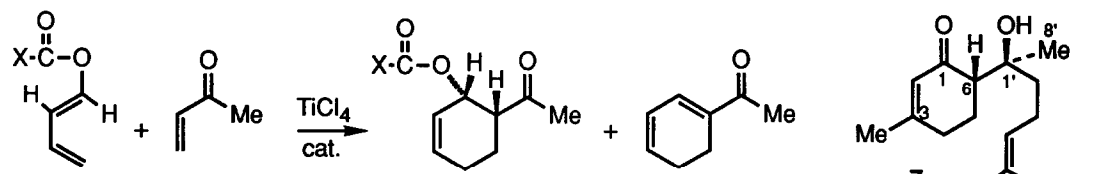
Summary: The $TiCl_4$-catalyzed addition of the title reactants to vinyl ketones regio- and stereospecifically yields *cis*-disubs. cyclohexenes which add RMgX stereospecifically to the ketone. A final product in this sequence is the intensely sweet sesquiterpene, hernandulcin.

A simple, often stereospecific synthesis of the first known *O*-(1,3-butadienyl) carbonates and carbamates from α,β-unsaturated aldehydes was outlined in the preceding paper.[1] Like 1-acetoxybutadiene,[2] the *E*-dienyl carbonate **1** only yields Diels-Alder adducts easily with quite activated dienophiles. The $TiCl_4$ catalyzed process[3] is more useful: **1E** reacts regio- and stereospecifically with the vinyl ketone **3** (excess, neat, 25 °C) to give the cyclohexene **4** in 68% yield. Michael elimination also occurs to form the diene **6** as a side product in 9% yield.[4] With the less electron withdrawing carbamate **2E**, the cycloaddition is faster and the adduct **5** is isolated in 92% yield along with 8% of **6**.[5]

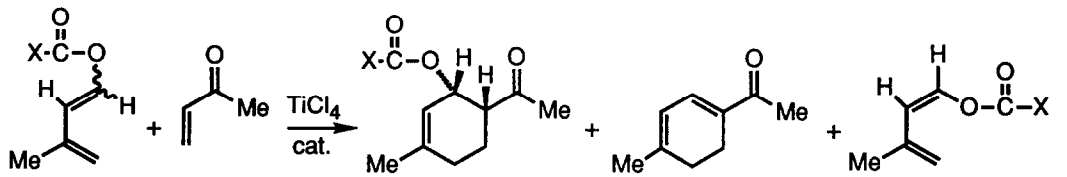


1E: X = OEt **3** **4**: X = OEt **6**
2E: X = NEt_2 **5**: X = NEt_2 (+)-Hernandulcin

The success of the transformation **2** → **5** encouraged us to test this process as the key to a general route to congeners of the sesquiterpene, (+)-hernandulcin (**7**),[6,7] isolated from a plant known to the Aztecs as Tzonpelic xihuitl or "sweet herb" (*Lippia dulcis* Trev.). To a human taste panel, **7** was judged over 1000 times sweeter than sucrose (not mutagenic or toxic to mice) although some aftertaste and a slight bitterness also were perceived.[6] Thus, **7** could be considered the prototype of a new class of dietary sucrose substitutes. In a previous synthesis of **7** by Kinghorn[6] from 3-methylcyclohexenone, (±)-**7** was contaminated by 5% of the $C^{1'}$ epimer. Another product is the self-aldol

adduct of 6-methyl-5-hepten-2-one[6] (15+% yield[8]). In the other route from (R)-limonene by Mori and Kato,[7] the product after 5 steps was a 1:1 mixture of **7** and its $C^{1'}$ epimer in 1% overall yield.

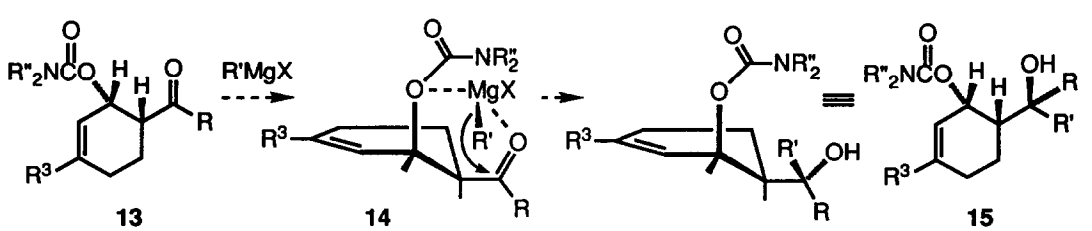
With this background, the $TiCl_4$ catalyzed reaction of **3** was repeated with the carbonate **8E,Z** and the carbamate **9E,Z**. When **8E,Z** was reacted with excess **3** and 0.01 equiv. of $TiCl_4$ at room temperature for 5 days, 83% of the original **8Z** was recovered pure. All of the **8E** was accounted for as the cycloadduct **10** (79% yield) and the cyclohexadiene **12** (20% yield). Similar treatment of **9E,Z** for two days afforded recovered **9Z** (76%), the desired cyclohexene **11** (89% yield based on **8E**) and only *ca.* 1% of the elimination product **12**. With 0.06 equiv. of $TiCl_4$, the reaction was faster and the yield of **11** was 88% but the amount of Michael elimination (→ **12**) increased to 11%. No cycloadduct was obtained when pure **9Z** was reacted with **3** and $TiCl_4$ for 8 days. Thus, in this Diels-Alder addition, only the sterically more accessible[9] *E*-diene undergoes reaction. The transformation also is completely regiospecific and stereospecific to give the "endo" isomer predicted by the Alder rule.



8E,Z: X = OEt **3** **10**: X = OEt **12** **8Z**: X = OEt

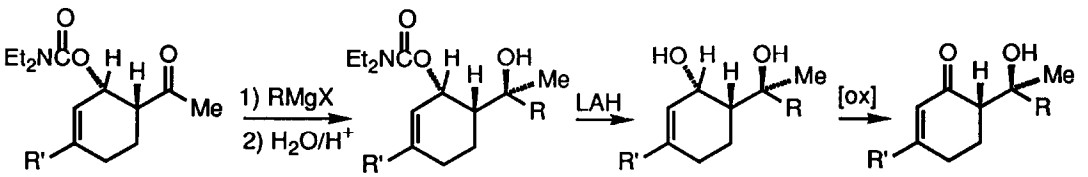
9E,Z: X = NEt_2 **11**: X = NEt_2 **9Z**: X = NEt_2

In adapting this chemistry to the production of analogues of **7**, the plan was to treat **13** with Grignard reagents to obtain **15** which after removal of the carbamate unit followed by oxidation would yield the desired products. In this synthetic strategy, the carbamate function in **13** was to play three critical roles besides protecting the latent carbonyl at C^1. First, compared with the keto function, the carbamate should be inert to the Grignard reagent. Second, if the carbamate and the carbonyl are simultaneously complexed to the Grignard magnesium, the Grignard alkyl should add to the carbon on the front face of the ketone carbonyl (see **14**). This "chelation control" has been observed in Grignard additions to *cis*-2acylcyclohexanols where the diastereofacial selectivity ordinarily is 100%.[10] Finally by including a chiral amine as part of the carbamate, it was hoped that significant enantioselectivity might be achieved in the adddition of the Grignard to the carbonyl. In related chemistry, chiral oxazolidinones (cyclic carbamates) have been used as reactants in the preparation of optically pure products by aldol condensations.[11]



13 **14** **15**

The temptations of enantioselectivity were deferred for later consideration. When the carbamate **11** was added to 1.2 equiv. of the Grignard reagent from commercial 5-bromo-2-methyl-2-pentene in THF at 0 °C, the racemic alcohol **16A** was isolated in 53% yield along with some recovered **11** (22%). None of the diastereomeric alcohol was found. With two equiv. of Grignard reagent, the yield of **16A** only increased to 59% and two side products were obtained.[12] When the alcohol **16A** was refluxed with 1.5 equiv of LAH for one hour, the carbamate group was removed and the diol **17A** was obtained in 99% yield. Subsequent oxidation of **17A** to (±)-**7** was less satisfactory. When this reaction was performed in CH_2Cl_2 with pyridinium chlorochromate adsorbed on alumina,[13] (±)-**7** (=**18A**) was isolated pure in 46% yield after flash chromatography. The IR ^1H NMR, and ^{13}C NMR spectral data for this product are in accord with the values given by Kinghorn and coworkers[6] for both natural (+)- and synthetic (±)-**7**.



5: A = H
11: A = Me

16

17

18

A: R=-$(CH_2)_2CH{=}CMe_2$, R'=-Me **B**: R=Bu, R'=Me

C: R=-$(CH_2)_2CH{=}CMe_2$, R'=H

The hernandulcin analogue **18B** also was made from **11**. Addition of 1.2 equiv. of commercial BuMgCl to **11** in THF at 0 °C gave the alcohol **16B** in 80% yield. Again reduction of **16B** was quantitative and the product diol **17B** was oxidized to the desired enone **18B** in 57% yield (46% overall yield from **11**). The structure-stereochemistry of **18B** was based in part on comparisons with the published NMR data for **7** and its diastereomer.[6,14] The 3-normethyl version of (±)-**7** also was prepared by the new route. As in the synthesis of **16A**, the Grignard addition to the ketone **5** was diastereofacially specific. The yield of alcohol **16C** was 70% using two equiv. of Grignard reagent. Again the LAH reductive removal of the carbamate was quantitative, but oxidation of **17C**, this time with MnO_2 in CH_2Cl_2 to **18C**[14] was not very satisfactory (48% yield, 34% overall from **5**). Thus the new scheme seems to presage a reasonably general route to congeners of **7**. Also, potential value of *O*-(1-butadienyl) carbamates in other synthetic applications is readily foreseen.

However, preparation of more analogues **18** ceased when **18** proved less stable in water than expected from ref. 6. Some decomposition even is observed after several days at room temperature in aqueous media.[8] The results implicate the reverse aldol fragmentation already noted[12] and other processes at $C^{1'}$. It is noteworthy that **7** continues to be publicized in the commercial sweetener area[15] although major structural changes will be required if it is to serve even as a useful lead.

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References and Notes

(1) De Cusati, P. F.; Olofson, R. A. *Tetrahedron Lett.* **1990**, preceding paper.

(2) Blanc, P.-Y *Helv. Chim. Acta* **1961**, *44*,1. Hill, R. K.; Carlson, R. M. *J. Org. Chem.* **1965**, *30*, 2414. Hirama, M.; Koyama, Y.; Shoji, Y.; Ito, S. *Tetrahedron Lett.* **1978**, 2289.

(3) For Lewis acid catalysis of Diels-Alder additions see: Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436. Fray, G. I.; Robinson, R. *Ibid.* **1961**, *83*, 249. Lutz, E. F.; Bailey, G. M. *Ibid.* **1964**, *86*, 3899. Williamson, K. L.; Hsu, Y.-F. L. *Ibid.* **1970**, *92*, 7385. Inukai, T.; Kojima, T. *J. Org. Chem.* **1970**, *35*, 1342; **1971**, *36*, 924. For more recent use of $TiCl_4$ and lit. see: Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256. The conversion **1** → **4** failed with $AlCl_3$ or BF_3.

(4) Also, treatment of **4** with Na_2CO_3 in aqueous dioxane afforded **6** in 87% yield.

(5) The products, **4**, **5**, **10**, and **11**, were assigned the *cis*-stereochemistry because J_{vic} for the methine protons is 4-5 Hz. For the *trans*-isomer to meet this spectral requirement, both substituents must be pseudoaxial. Subsequent transformations of **11** confirm the stereochemical assignment which follows the Alder rule.[3]

(6) Compadre, C. M.; Pezzuto, J. M.; Kinghorn, A. D.; Kamath, S. K. *Science* **1985**, *239*, 417; Compadre, C. M.; Hussain, R. A.; Lopez de Compadre, R. L.; Pezzuto, J. M.; Kinghorn, A. D. *J. Agric. Food Chem.* **1987**, *35*, 273.

(7) Mori, K.; Kato, M. *Tetrahedron Lett.* **1986**, *27*, 981; *Tetrahedron* **1986**, *42*, 5895. However, this route to **7** did establish the absolute (6S,1'S)-stereochemistry.

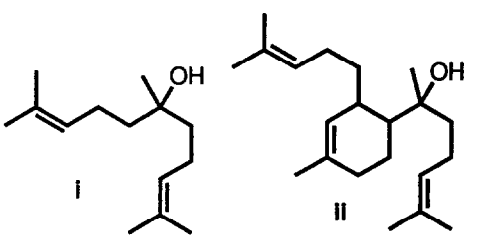
(8) Communicated by G. P. Wooden and J.-P. Senet at SNPE; also reproduced by us.

(9) Craig, D. J. *J. Am. Chem. Soc.* **1950**, *72*, 1678. Grummitt, O.; Christoph, F. *Ibid.* **1951**, *73*, 3479.

(10) Ghera, E.; Shoua, S. *J. Org. Chem.* **1972**, *37*, 1292.

(11) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375. Morrison, J. D.; Mosher, H. S.; Asymmetric Organic Reactions; Prentice-Hall: New Jersey, **1971**, pp 252-257; and refs. therein.

(12) The major side product **I** (14% yield) should be formed by Grignard addition to 6-methyl-5-heptene-2-one, a retroaldol fragmentation product of **11**. Displacement by the Grignard at C^1 of **16A** would generate **II** (3% yield). Neither **I** nor **II** was found when less Grignard reagent was used. For more on the retroaldol condensation see the last paragraph of the text.



I II

(13) Cheng, Y.-S.; Liu, W.-L.; Chen, S. *Synthesis* **1980**, 223.

(14) For example in **7**, the four ^{13}C NMR signals which distinguish it from its diastereomer are found at 52.0 (C^6), 40.1 ($C^{2'}$), 25.0 (C^5), and 23.6 ($C^{8'}$) ppm.[6] The same values for **18B** are 52.0 (C^6), 40.1 ($C^{2'}$), 25.0 (C^5), and 23.8 ($C^{8'}$) ppm. For **18C**, the values are 53.3 (C^6), 39.9 ($C^{2'}$), 25.1 (C^5), and 23.5 ($C^{8'}$) ppm.

(15) *Chem. Eng. News* Jan. 28, **1985**, p37. Goodburn, K. E. "A Users Guide to the New Sweeteners - An Update"; Leatherhead Food RA: London, **1987**. *Manufacturing Chemist* July **1987**, p45. Mandrile, E. L.; Bongiorno de Pfirter, G. M.; Cortella, A. *Acta Farm. Bonaerense* **1988**, *7*, 117. Also see: Compadre, C. M.; Hussain, R. A.; Lopez de Compadre, R. L.; Pezzuto, J. M.; Kinghorn, A. D.; *Experientia* **1988**, *44*, 447.

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