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(5S)-1,1-Diethoxy-5-*t*-butyldiphenylsilyloxy-hex-3-en-2-one: a new functionalized versatile chiral building block

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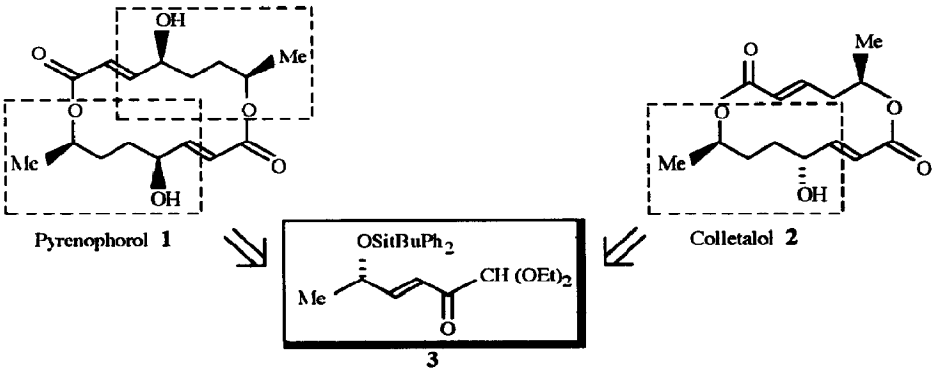
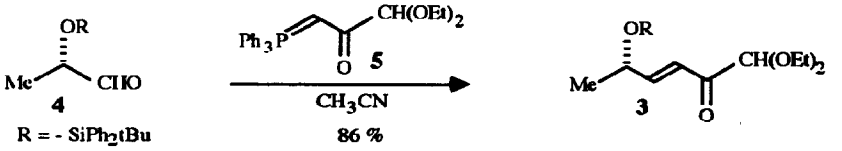
ABSTRACT : *The title enone 3 is easily prepared from protected lactaldehyde. Highly diastereoselective reduction of 3 is only obtained with CBS reagents.*

Macrodiolides are very interesting natural products, both from the chemical and biological points of view.[1] They can be divided in two groups : the symmetrical 16 membered compounds with pyrenophorol **1** as a representative example and non symmetrical 14 membered derivatives such as colletalol **2**. Some years ago, we started a program dealing with the search for a ***general*** strategy towards both classes of natural macrodiolides, their diastereoisomers and some selected structural analogs. We have already shown, on simple models, that the use of two consecutive Wittig reactions is particularly efficient for building macrodiolides of any desired ring size.[2] Taking advantage of this approach, we have now designed the new chiral, non racemic, enone **3** as a versatile key intermediate[3,4]. It is not only a very convenient fragment for both series but the enone functionality should also allow the introduction of various substituents at the desired positions of the required analogs.



The purpose of this Letter is to report our preliminary results in this field with the synthesis of enone **3** and a few functional modifications, with special regard to the diastereoselectivity of the carbonyl group reduction.

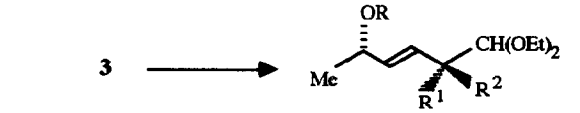
The enone **3** is easily prepared by Wittig reaction of protected lactaldehyde **4** [5] with the known phosphorane **5**.[6] It is isolated in 86 % yield after chromatography and fully characterized by spectral and analytical data.[7]



The optical purity of enone **3** has been established via its corresponding Mosher's ester after deprotection to the secondary alcohol by $Bu_4N^+F^-$ in the presence of acetic acid (1 eq.)[8] followed by esterification with Mosher's acid.[9] ^1H NMR analysis indicated that this ester was a 97/3 mixture of diastereoisomers, thus establishing a 94 % d.e. for **3**.[10]

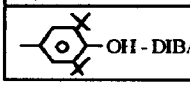
The control of the diastereoselectivity during the reduction of the carbonyl group in enone **3** was examined first. Although 1,4-addition reactions on γ-alkoxy protected enones have been studied in detail,[11] it is interesting to point out that very few studies concerning the 1,2-addition to such derivatives have been reported. High diastereoselectivities have been observed only in a few cases with complex systems bearing many extra stereogenic centers,[12] having more rigid bicyclic systems [13] or having peculiar conformational properties.[14] The reduction is usually non stereoselective on linear more flexible systems, as in the synthesis of thromboxane B_2,[15] its thia analog [16] or other arachidonic acid metabolites.[17]

The reduction of simple acyclic γ-methoxy enones was also found non stereoselective, thus excluding a vinylogous version of Cram's rule.[18] However, taking into account the novelty of structure **3** and especially the presence of the bulky silyl ether protecting group, it was of interest to perform a brief systematic study of the 1,2-reduction.



R = - SiPh2tBu **6** : R^1 = H, R^2 = OH ; **7** : R^1 = OH, R^2 = H

Table 1

Reaction	Yield (%)	6/7
$NaBH_4$ - EtOH - 0°C	75	58 : 42
$NaBH_4$ - EtOH - H_2O - 0°C	99	50 : 50
$NaBH_4$ - $CeCl_3$ - MeOH - 30°C	86	53 : 47
LS - Selectride - 78°C	50	33 : 67
DIBAL-H - -78°C	50	48 : 52
 OH - DIBAL-H	61	48 : 52

As shown on table 1, all attempts to use non-chiral, even bulky, reagents gave very little, or no, asymmetric induction during the 1,2-reduction : mixtures of diols **6** and **7** being obtained in each case (NMR analysis).

We then turned to chiral reducing agents (table 2)[19]. While (S)-alpine borane gave both a poor yield and a low d.e., good results were obtained using oxazaborolidines. As expected from literature data, best diastereoselectivities were obtained using CBS reagents [20,21]. Starting from each enantiomer, it is possible to obtain in good overall yield and with an excellent diastereoselectivity both diastereoisomers **6** or **7**.[22]

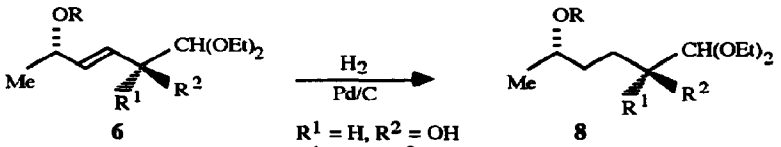
The absolute configuration of the newly created stereogenic center has been attributed by analogy with results already obtained with several other enones ; for instance, in the prostaglandin series CBS reagents from (S)-diphenylprolinol gave an (R)-alcohol.[20,23]

Table 2

Reaction	Yield (%)	6/7
(S)-Alpine borane neat - two weeks	40	60 : 40
(S)-diphenyl prolinol - BH_3 - Me_2S	92	12 : 88
(R)-diphenyl prolinol - BH_3 - Me_2S	95	90 : 10
(S) - CBS reagent [(a)]	85	5 : 95
(R) - CBS reagent [(b)]	87	97 : 3

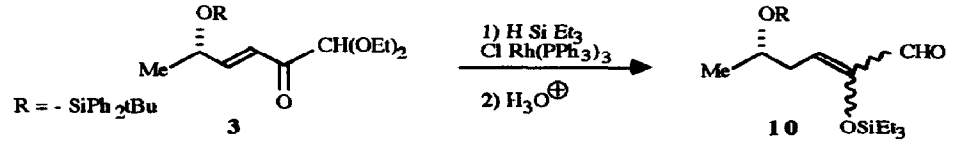
[(a)] oxazaborolidine obtained from (S)-diphenylprolinol and *n* Bu B(N*i* $Pr_2)_2$;
[(b)] oxazaborolidine obtained from (R)-diphenylprolinol and *n* Bu B(N*i* $Pr_2)_2$.

Catalytic hydrogenation (H_2, Pd/C, 67 % yield) of the double bond leads cleanly to the monoprotected diols **10** and **11** required for macrodiolide synthesis.



6 R^1 = H, R^2 = OH **8**
7 R^1 = OH, R^2 = H **9**

It is also interesting to note that hydrosilylation of **3**, in the presence of Wilkinson's catalyst gave, after acidic work up, the corresponding silyl enol ether aldehyde **10** (32 % non optimized yield).[24] This new type of intermediate should be useful for the preparation of macrodiolides substituted in the 3-position.



In conclusion, the enone **3** is a new, easily accessible, versatile intermediate. Due to its functionalization, it may be useful not only in the synthesis of macrodiolides but also for many other types of molecules.

Acknowledgements: We thank Drs. P.Y. Chavant and M. Vaultier for fruitful informations concerning CBS reagents, Drs. A. Fauvé and H. Veschambre for the experiments with *Beauveria sulfurescens*, Drs. J.P. Lellouche and D. Bremner for useful discussions and S. Amigoni for helpful measurement. H.D. thanks CNRS and Roussel-Uclaf for a fellowship.

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2 - Yvergnaux F., Le Floc'h Y., Grée R., *Tetrahedron Lett.*, 1989, **30**, 7397-7398 ; ibidem, *Bull. Soc. Chim. Fr.*, 1992, **129**, 62-70.

3 - Note that, although we used the cheaper (S) lactate as starting material for this study, control of the absolute configuration at the secondary alcohol position bearing the methyl group is easy. It is possible to start either with the (R) lactate, or alternatively, invert the absolute configuration at this stereocenter using a Mitsunobu-type reaction later in the synthesis.This has been shown by the synthesis of natural colletalol and its 11-(S) diastereoisomer.[4]

4 - H. Dumartin, Thesis, University of Rennes, September 1993.

5 - Hopkins M. H., Hoverman L. E., Rishton G. M., *J. Am. Chem. Soc.*, 1991, **113**, 5354-5365 ; Suhail K. M., Hawkins L. D., Braker D. C., *J. Org. Chem.*, 1983, **48**, 5180-5182.

6 - Le Corre M., ***Bull. Soc. Chim. Fr.***, 1974, **9-10**, 1951-1955.

7 - Colourless oil. IR (NaCl, film, ν cm^{-1}) : 1700 (C=O) ; 1625 (C=C). $[\alpha]_D^{20}$ = -57° (c = 0.04 , CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ ppm) : 7.8-7.3 (m, 10H arom.) ; 7.01 (dd, 1H, H_4, J = 15.7 ; 4.4 Hz); 6.68 (dd, 1H, H_3, J = 15.7 ; 1.7 Hz) ; 4.75 (s, 1H, H_1) ; 4.48 (qdd, 1H, H_5, J = 6.6 ; 4.4 ; 1.7 Hz) ; 3.8-3.4 (m, 4H, CH_2) ; 1.24 (t, 3H, CH_3, J = 7.1 Hz) ; 1.23 (t, 3H, CH_3, J = 7.1 Hz) ; 1.16 (d, 3H, CH_3, J = 6.6 Hz) ; 1.09 (s, 9H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ) : 194.7 (C_2) ; 151.9 (C_4) ; 135.8 ; 134.0 ; 133.4 ; 129.8 ; 127.6 (C arom.) ; 122.3 (C_3) ; 101.9 (C_1) ; 69.1 (C_5) ; 62.7 and 62.6 (CH_2) ; 27.0 (CH_3) ; 23.2 (CH_3) ; 19.3 (Si-C) ; 15.2 (CH_3).

8 - Ogilvie K.K., Beaucage S. L., Schifman A. L., Theriault N. Y., Sadana K. L., *Can. J. Chem.*, 1978, **56**, 2768-2780.

9 - The esterification was accomplished using Steglich's method : Neises B., Steglich W., ***Angew. Chim. Int. Ed. Engl.***, 1978, **17**, 522-524.

10 - This was done by comparison with an authentic reference sample obtained from racemic lactaldehyde (±)-**4**. Particularly relevant are the ^1H NMR signals at 1.50 and 1.42 ppm.

11 - See for instance : Bernardi A., Capelli A. M., Gennari C., Scolastico C., *Tetrahedron Asym.*, 1990, **1**, 21-32 and references therein.

12 - Jarosz S., ***Tetrahedron Lett.***, 1988, **29**, 1193-1196.

13 - Garlaschelli L., Vidari G., *Tetrahedron*, 1989, **45**, 7371-7378.

14 - Still W.C., Murata S., Revial G., Yoshihara K., *J. Am. Chem. Soc.*, 1983, **105**, 625-627.

15 - Hanessian S., Lavallee P., *Can. J. Chem.*, 1977, **55**, 562-565.

16 - Kale V.N., Cline D.L.V., *J. Org. Chem.*, 1984, **49**, 1554-1563.

17 - Just G., Oh H., *Can. J. Chem.*, 1981, **59**, 2729-2736.

18 - Fleming I., Kühne M., Takaki K., *J. Chem. Soc., Perkin Trans I.*, 1986, 725-728.

19 - It is interesting to note that no reduction of **3** was observed using *Beauveria sulfurescens*, a fungus usually effective for the reduction of enones : Fauvé A., Renard M.F., Veschambre H., *J. Org. Chem.*, 1987, **52**, 4893-4897.

20 - Corey E.J., Bakshi R.K., Shibata S., *J. Am. Chem. Soc.*, 1987, **109**, 5551-5553 ; Corey E. J., Bakshi R. K., *Tetrahedron Lett.*, 1990, **31**, 611-614.

21 - The oxaborolidines were prepared by a new, recently described, procedure : Chavant P. Y., Vaultier M., *J. Organomet. Chem.*, 1993, **455**, 37-46.

22 - (S)-**6** : $[\alpha]_D^{20}$ =-15.4° (c = 0.04 , CH_2Cl_2) ; ^1H NMR (300 MHz, $CDCl_3$, δ ppm) : 7.8-7.4 (m, 10H arom.) ; 5.85 (ddd, 1H, H_4, J = 15.6 ; 5.9 ; 1.3 Hz) ; 5.62 (ddd, 1H, H_3, J = 15.6 ; 5.7 ; 1.2 Hz) ; 4.4-4.3 (m, 1H, H_5) ; 4.16 (d, 1H, H_1, J = 6.2 Hz) ; 4.1-4.0 (m, 1H, H_2) ; 3.9-3.4 (m, 4H, H_9) ; 2.15 (d, 1H, OH, J = 3.3 Hz) ; 1.23 (t, 3H, H_{10}, J = 7.0 Hz) ; 1.17 (t, 3H, $H_{10'}$, J = 7.0 Hz) ; 1.14 (d, 3H, H_6, J = 6.4 Hz) ; 1.06 (s, 9H, H_8). ^{13}C NMR (22.5 MHz, $CDCl_3$, δ ppm) : 136.9 (C_4) ; 136.0 et 135.9 (C_o) ; 134.6 and 134.3 (C_q) ; 129.5 (C_p) ; 127.5 (C_m) ; 126.1 (C_3) ; 104.8 (C_1) ; 72.1 (C_2) ; 69.7 (C_5); 63.7 et 63.4 (C_9) ; 27.0 (C_8) ; 24.2 (C_6) ; 19.3 (C_7) ; 15.4 (C_{10}).
(R)-**7** : $[\alpha]_D^{20}$ =-38.1°(c = 0.04 , CH_2Cl_2) ; ^1H NMR (300 MHz, $CDCl_3$, δ ppm) : 7.8-7.4 (m, 10H arom.) ; 5.84 (ddd, 1H, H_4, J = 15.4 ; 5.8 ; 1.4 Hz) ; 5.64 (ddd, 1H, H_3, J = 15.5 ; 5.6 ; 1.2 Hz) ; 4.4-4.3 (m, 1H, H_5) ; 4.19 (d, 1H, H_1, J = 6.0 Hz) ; 4.1-4.0 (m, 1H, H_2) ; 3.9-3.4 (m, 4H, H_9) ; 2.23 (d, 1H, OH, J = 3.4 Hz) ; 1.23 (t, 3H, H_{10}, J = 7.1 Hz) ; 1.17 (t, 3H, $H_{10'}$, J = 7.1 Hz) ; 1.13 (d, 3H, H_6, J = 6.4 Hz) ; 1.06 (s, 9H, H_8). ^{13}C NMR (22.5 MHz, $CDCl_3$, δ ppm) : 136.6 (C_4) ; 136.0 et 135.8 (C_o) ; 134.6 and 134.2 (C_q) ; 129.5 (C_p) ; 127.5 (C_m) ; 126.2 (C_3) ; 104.7 (C_1) ; 72.0 (C_2) ; 69.7 (C_5) ; 63.4 (C_9) ; 27.0 (C_8) ; 24.2 (C_6) ; 19.3 (C_7) ; 15.4 (C_{10}).

23 - See for instance : Corey E.J., Bakshi R.K., Shibata S., Chen C. P., Singh V. K., *J. Am. Chem. Soc.*, 1987, **109**, 7925-7926 ; Corey E. J., Kigoshi H., *Tetrahedron Lett.*, 1991, **32**, 5025-5028.

24 - This reaction is highly stereoselective but the stereochemistry of the major isomer has not yet been unambiguously established.

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