Synthesis of Perhydrooxazinones from 2-Aza-3-Trimethylsilyloxy-1,3-Butadiene. A General Route to 3,3-Disubstituted-β-Hydroxy Acids

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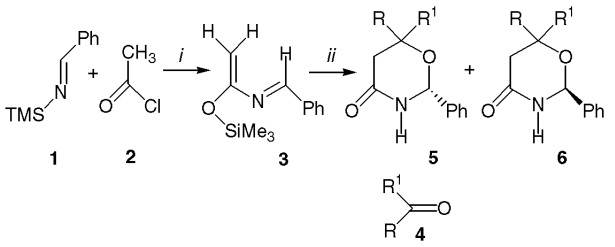
Abstract: 1-Phenyl-2-aza-3-trimethylsilyloxy-1,3-butadiene reacts with aliphatic, aromatic and cyclic ketones to give in good to excellent yields 6,6-disubstituted-1,3-perhydro-oxazin-4-ones which, in turn, have been readily converted into β-hydroxy carboxylic acids.

Key words: Diels-Alder reactions, carboxylic acids, heterocycles, azo compounds

The hetero Diels-Alder reaction using carbonyl compounds as dienophiles is a very useful method to construct heterocyclic rings and is widely used as a key step in the synthesis of natural products.[1]

In conjunction with our current efforts on the use of 2-aza-3-silyloxy-1,3-dienes,[2] derived from *N*-trialkylsilylimines[3] and acyl chloride (Scheme 1), as useful tools in organic synthesis for the preparation of nitrogen containing heterocycles, we have demonstrated the utility of a stable 2-aza-3-trialkylsilyloxy-1,3-butadiene in selectively generating *cis*-,[4] *trans*-β-lactams,[5] 5-amido-perhydro-oxazinones, precursors of α-amino-β-hydroxy acids[6] and tetramic acids analogues.[7]

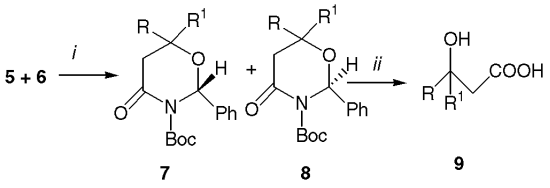
In this paper we report our preliminary results on the synthesis of 6,6-disubstituted perhydro-oxazinones using the same approach.



Reagents and Conditions: *i*: NEt_3, heptane: *ii*: BF_3, Et_2O, -78ºC, CH_2Cl_2.

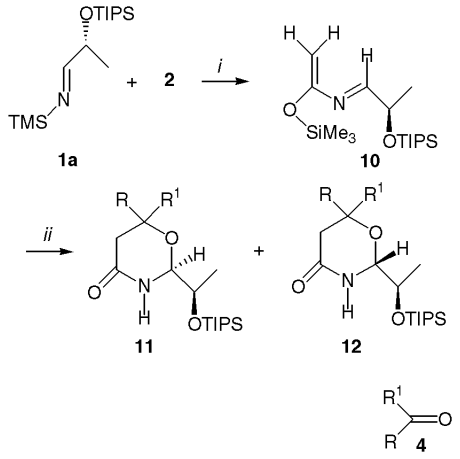
Scheme 1

Treatment of the intermediate **3** (Scheme 1), obtained from *N*-trimethylsilylbenzaldimine **1** and acetyl chloride **2**, with ketones **4a-i** in the presence of BF_3 etherate in dichloromethane at -78°C for 3 h, followed by stirring overnight at r.t., afforded the corresponding 6,6-disubstituted-tetrahydro-1,3-oxazin-4-ones **5a-i** and **6b-f** in yields ranging from 45 to 90% (Table 1).[8,9] No reaction occurred on mixing the azadiene **3** with ketone **4a** in dichloromethane at room temperature. This new strategy allows the preparation of perhydro-oxazinones and their transformation into an important class of biologically interesting compounds: the 3,3-disubstituted-β-hydroxy acids.[10] As a matter of fact, elaboration of the diastereomeric mixture of the perhydro-oxazinones **5a-i** and **6b-f** into Boc derivatives **7a-i** and **8b-f** (di-*t*-butylpyrocarbonate, TEA, $DMAP_{cat}$) and treatment of such compounds with LiOH in $EtOH/H_2O$ solution, afforded the β-hydroxy-acids **9a-i** in almost quantitative yields as a racemic mixture (Scheme 2).[11,9]



Reagents and Conditions. *i*: $O[CO_2C(CH_3)_3]_2$, NEt_3, $DMAP_{cat}$, CH_2Cl_2; *ii* : LiOH, $EtOH/H_2O$.

Scheme 2



Reagents and Conditions: *i*: NEt_3, heptane: *ii*: BF_3, Et_2O, -78ºC, CH_2Cl_2.

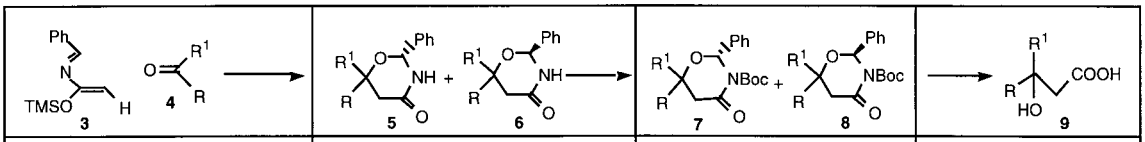
11a/12a: R=R^1=CH_3: Diastereomeric ratio 48/52; 53% yield

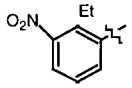
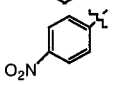
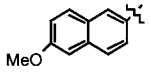
11b/12b: R-R^1=Cyclohexyl: Diastereomeric ratio 50/50; 63% yield

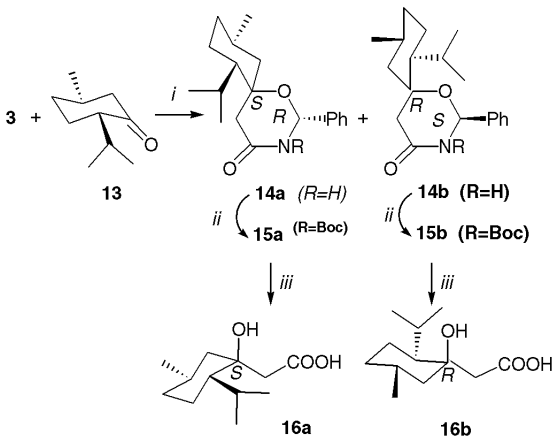
11c: R=Me; R^1=Ph: Inseparable mixture of stereoisomers; 40% yield

Scheme 3

Table 1 3,3-Disubstituted-3- hydroxy-acids from 1-phenyl- 2-aza-3-trimethylsilyloxy-1,3-butadiene



Ketones	R	R1	Products	Ratio	Yield%	Products	Yield%	Product	Yield%
4a	Me	Me	5a	-----	73	7a	91	9a	91
4b	Me	Ph	5b/6b	74/26	69	7b/8b	93	9b	96
4c	Me	Et	5c/6c	33/66	55	7c/8c	78	9c	83
4d	Me		5d/6d	42/58	75	7d/8d	76	9d	45
4e	Me		5e/6e	46/54	65	7e/8e	98	9e	86
4f	Me		5f/6f	75/25	64	7f/8f	90	9f	87
4g			5g	-----	45	7g	84	9g	96
4h			5h	--	90	7h	95	9h	59
4i			5i	--	70	7i	80	9i	91



Reagents and Conditions: *i*: $BF_3\langle Et_2O$, -78ºC, CH_2Cl_2 (Overall yield 54%; Ratio **14a**/**14b**=91/9); *ii*: $O[CO_2C(CH_3)_3]_2$, NEt_3, $DMAP_{cat}$, CH_2Cl_2; *iii*: LiOH, $EtOH/H_2O$.

Scheme 4

The possibility of preparing, by this route, optically pure β-hydroxy perhydro-oxazinones and, therefore, β-hydroxy acids has been tested using optically pure starting material as diene or dienophile. Preliminary results obtained using the homochiral azadiene **10**, derived from (*S*)-triisopropylsilyloxy-*N*-trimethylsilylimine **1a** and acetyl chloride, have not shown any appreciable diastereoselectivity (Scheme 3) since the corresponding 1/1 diastereomeric mixtures of 1,3-oxazine-4-ones **11a-b** and **12a-b** have been obtained.

In contrast the use of the optically pure (-)-menthone **13** as dienophile achieved a very high diastereoselectivity (Scheme 4).[12] The perhydro-oxazinones **14a** and **14b** thus obtained have been converted into optically pure β-hydroxy-acids **16a** and **16b** (Scheme 4).

Work is in progress in this vein as well as on the use of chiral catalysts, targeting the synthesis of optically pure 3,3-disubstituted-3-hydroxy acids.

Acknowledgement

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(7) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M.; Piersanti, G. *Tetrahedron:Asymm.* **1999**, *10*, 1445.
(8) ***Synthesis of Perhydro-oxazin-4-ones: General procedure***
To a solution of LiHMDSA (1 ml of 1M solution in THF) at 0°C benzaldehyde or (*S*)-triisopropylsilyloxy lactaldehyde (1mmol) in heptane (5 ml) was added. The reaction mixture was allowed to reach r.t. spontaneously while the stirring was continued for 1h. TMSCl (1.1 mmol) was added in one portion at 0°C and the reaction mixture further stirred for 1 h. A white precipitate formed. The solution was cooled at 0°C and NEt_3 (2 mmol) was added in one portion. The acetyl chloride **3** (1 mmol) was added dropwise. Stirring was maintained for 1/2 h at 0°C and 1/2 h at r.t. while a new copious precipitate appeared. The precipitate was filtered under argon, the solvent removed *in vacuo* and to the resulting oily residue CH_2Cl_2 (10 ml) was added and the solution cooled at -78°C. Ketone **4** in CH_2Cl_2 (2 ml) was added followed by BF_3 Et_2O (1.1 mmol) in CH_2Cl_2 (5 ml). The solution was stirred overnight while the temperature was allowed to reach r.t.. The mixture was poured into 5% $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2 . The organic layers were dried and the solvent removed *in vacuo*. Flash chromatography of the residue (CH_2Cl_2 /acetone 9/1) yielded pure isolated perhydro-oxazin-4-ones.
(9) All compounds, identified as pure isolated compound, gave analytical data (I.R., ^1H and ^{13}C NMR, MS and E.A.) consistent with the assigned structures and literature data. The configuration of each isomer has been determined by means of NOE experiments. Selected data as follows: (^1H NMR: 200 MHz, $CDCl_3$, *ppm* ; ^{13}C NMR 50 MHz, $CDCl_3$, *ppm*). **3**: ^1H NMR 8.42 (s, 1H), 7.85 (m, 2H), 7.42 (m, 3H), 4.68 (s, 1H), 4.30 (s, 1H), 0.30 (s, 9H); ^{13}C NMR 156.83, 156.44, 135.93, 131.08, 128.94, 128.57, 91.64, -0.13. **5a**: m.p.=98-100°C; ^1H NMR 7.36 (m, 5H), 7.10 (s, 1H), 5.72 (s, 1H), 2.44 (d, 1H, J=16.8), 2.28 (d, 1H, J=16.8) 1.38 (s, 3H), 1.30 (s, 3H); ^{13}C NMR 169.38, 138.29, 129.40, 128.61, 126.72, 80.26, 73.12, 43.22, 29.28, 24.22; **5b** (*trans* Me-H2): m.p.=176-8°C; ^1H NMR 7.40 (m, 10H), 6.70 (s, 1H), 5.25 (s, 1H), 3.11 (d, 1H, J=16.85), 2.76 (d, 1H, J=16.85), 1.60 (s, 3H); ^{13}C NMR 168.89, 141.71, 137.80, 129.29, 128.57, 128.44, 127.79, 126.54, 125.54, 80.61, 77.04, 40.85, 31.73; **6b** (*cis* Me-H2): m.p.= 156-8°C; ^1H NMR 7.40 (m, 10H), 6.36 (s, 1H), 6.00 (s, 1H), 2.80 (s, 2H), 1.73 (s, 3H); ^{13}C NMR 168.70, 146.00, 138.23, 129.70, 128.86, 128.42, 127.34, 126.87, 124.12, 80.46, 76.46, 43.87, 25.77; **5c** (*trans* Me-H2): m.p.=103-5°C; ^1H NMR 7.42 (m, 5H), 6.10 (s, 1H), 5.73 (s, 1H), 2.48 (s, 2H), 1.88 (sextet, 1H, J=7.38), 1.65 (sextet, 1H, J=7.38), 1.30 (s, 3H), 1.00 (t, 3H, J=7.38; ^{13}C NMR 169.73, 138.20, 129.73, 128.91, 126.77, 80.33, 75.83, 42.57, 30.18, 26.38, 7.81; **6c** (*cis* Me-H2) m.p.=82-4°C; ^1H NMR 7.42 (m, 5H), 6.35 (s, 1H), 5.80 (s, 1H), 2.53 (d, 1H, J=16.75), 2.30 (d, 1H, J=16.75), 1.65 (q, 2H, J=7.45), 1.39 (s, 3H), 0.96 (t, 3H, J=7.45); ^{13}C NMR 169.59, 138.42, 129.61, 128.81, 126.74, 80.20, 75.50, 41.63, 35.37, 22.38, 7.63; **5d** (*trans* Me-H2): m.p.=184-6°C; ^1H NMR 8.34 (t, 1H, J=2.02), 8.20 (m, 1H), 7.76 (m, 1H), 7.60 (t, 1H, J=7.95), 7.43 (s, 5H), 6.48 (s, 1H), 5.40 (s, 1H), 3.13 (d, 1H, J=16.64), 2.91 (d, 1H, J=16.64), 1.65 (s, 3H); ^{13}C NMR 168.37, 145.45, 137.25, 131.53, 130.08, 129.01, 126.73, 124.00, 120.82, 81.31, 77.07, 41.62, 32.14; **6d** (*cis* Me-H2): m.p.=145.7 °C; ^1H NMR 8.34 (t, 1H, J=2.08), 8.15 (m, 1H), 7.78 (m, 1H), 7.50 (m, 6H), 6.55 (s, 1H), 6.05 (s, 1H), 2.94 (d, 1H, J=16.35), 2.82 (d, 1H, J=16.35), 1.80 (s, 3H); ^{13}C NMR 167.96, 148.08, 137.46, 130.36, 129.93, 129.51, 128.96, 126.82, 122.42, 119.64, 80.60, 76.13, 43.61, 26.07; **5e** (*trans* Me-H2): m.p.= 190-2°C; ^1H NMR 8.27 (d, 2H, J=8.75), 7.63 (d, 2H, J=8.75), 7.44 (s, 5H), 6,32 (s, 1H), 5.39 (s, 1H), 3.12 (d, 1H, J=16.68), 2.92 (d, 1H, J=16.68), 1.66 (s, 3H); ^{13}C NMR 168.32, 150.30, 147.76, 137.25, 130.11, 129.05, 126.72, 126.68, 124.21, 81.41, 77.25, 41.76, 32.01; **6e** (*cis* Me-H2): m.p. =204-6 °C; ^1H NMR 8.20 (d, 2H, J=8.70), 7.62 (d, 2H, J=8.70), 7.35 (m, 5H), 6.68 (s, 1H), 6.02 (s, 1H), 2.90 (d, 1H, J=16.60), 2.79 (d, 1H, J=16.60), 1.76 (s, 3H); ^{13}C NMR 167.79, 152.88, 147.27, 137.54, 130.07, 129.05, 126.85, 125.32, 123.76, 84.64, 77.03, 43.57, 26.06; **5f** (*trans* Me-H2): m.p.=84-86°C; ^1H NMR 7.75 (m, 3H), 7.60 (m, 2H), 7.35 (s, 5H), 7.15 (m, 2H), 6.10 (s, 1H), 5.13 (s, 1H), 3.90 (s, 3H), 3.25 (d, 1H, J=17.10), 2.85 (d, 1H, J=17.10), 1.68 (s, 3H); ^{13}C NMR 168.99, 158.33, 138.10, 136.68, 136.64, 134.18, 129.83, 129.70, 128.80, 128.45, 127.84, 126.85, 124.81, 124.30, 119.23, 105.69, 81.10, 77.50, 55.34, 41.18, 31.74; **6f** (*cis* Me-H2): m.p.= 130-2°C; ^1H NMR 7.80- 7.10 (m, 11H), 6.43 (s, 1H), 6.10 (s, 1H), 3.90 (s, 3H), 2.93 (s, 2H), 1.82 (s, 3H); ^{13}C NMR 168.67, 157.92, 141.00, 138.25, 133.78, 129.81, 129.75, 128.85, 127.15, 126.96, 123.17, 122.62, 119.06, 105.60, 80.66, 76.67, 53.31, 43.94, 25.82; **5g**: m.p. =118-20°C; ^1H NMR 7.40 (m, 5H), 6.90 (s, 1H), 5.75 (s, 1H), 2.68 (d, 1H, J= 16.90), 2.37 (d, 1H, J= 16.90), 2.15 (m, 1H), 2.05-1.50 (m, 7H); ^{13}C NMR 169.54, 138.42, 129.46, 128.67, 126.72, 83.91, 80.68, 41.25, 39.92, 34.02, 23.83, 22.80; **5h**: m.p.=136-8°C; ^1H NMR 7.40 (m, 5H), 6.90 (s, 1H), 2.32 (s, 2H), 2.00 (m, 2H), 1.50 (m, 8H); ^{13}C NMR 169.49, 138.44, 128.99, 128.34, 126.45, 79.11, 73.79, 42.17, 38.24, 32.16, 25.12, 21.47, 21.31; **5i**: m.p.=124-6 °C; ^1H NMR 7.40 (m, 5H), 6.45 (s, 1H), 5.74 (s, 1H), 2.40 (s, 2H), 2.05-1.35 (m, 12H); ^{13}C NMR 169.78, 138.43, 129.55, 128.80, 126.74, 79.88, 78.36, 43.25, 42.33, 36.02, 29.45, 29.33, 21.77, 21.61; **11a**: ^1H NMR 6.35 (s, 1H), 4.47 (d, 1H, J= 6.84), 3.78 (quintet, 1H, J= 6.16), 2.30 (m, 2H), 1.30 (s, 6H), 1.25 (d, 3H, J=6.06), 1.08 (s, 21H); ^{13}C NMR 168.56, 82.04, 72.33, 71.09, 43.32, 29.41, 23.77, 19.15, 17.82, 12.33. **12a**: ^1H NMR 6.15 (s, 1H), 4.90 (d, 1H, J= 3.40), 4.00 (dq, 1H, J= 3.40, 6.12), 2.30 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H), 1.12 (d, 3H, J= 6.12), 1.04 (s, 21H); ^{13}C NMR 168.76, 79.98, 72.33, 69.10, 43.24, 29.41, 23.20, 17.72, 15.45, 11.93. **11b**: ^1H NMR 6.32 (s, 1H), 4.36 (d, 1H, J= 6.82), 3.75 (quintet, 1H, J= 6.16), 2.22 (s, 2H), 1.90- 1.30 (m, 10H), 1.23 (d, 3H, J= 6.16), 1.00 (s, 21H); ^{13}C NMR 169.06, 81.47, 73.60, 71.69, 43.02, 38.39, 31.91, 21.64, 21.56, 21.53, 19.68, 18.10, 12.62. **12b**: ^1H NMR 6.12 (s, 1H), 4.88 (d, 1H, J= 3.20), 4.02 (dq, 1H, J=3.20 6.16), 2.28 (s, 2H), 1.90 (m, 1H), 1.70- 1.20 (m, 9H), 1.13 (d, 3H, J= 6.16), 1.04 (s, 21H); ^{13}C NMR 169.06, 79.33, 73.60, 69.35, 42.73, 38.31, 31.75, 25.39, 21.51, 17.97, 15.68, 12.19. **14a**: m.p.=160-2°C; $[\alpha]_D^{20}$=+38.75 (c=0.96 $CHCl_3$); ^1H NMR 7.40 (m, 5H), 6.40 (s, 1H), 5.83 (d, 1H, J= 3.66), 3.25 (d, 1H, J= 14.94), 2.15 (m, 2H), 1.80 (m, 3H), 1.50 (m, 2H), 1.10-0.75 (m, 12H); ^{13}C NMR 172.14, 137.90, 129.41, 128.83, 126.41, 81.33, 78.17, 49.74, 49.68, 41.08, 34.90, 27.75, 26.24, 23.74, 22.18, 21.27, 17.66; **14b**: m.p.= 174-6°C; $[\alpha]_D^{20}$=-64.37 (*c*= 0.32 $CHCl_3$); ^1H NMR 7.40 (m, 5H), 6.10 (s, 1H), 5.71 (d, 1H, J=1.96), 2.79 (d, 1H, J=16.78), 2.12 (m, 3H), 1.70 (m, 2H), 1.55 (m, 3H), 1.20-0.80 (m, 11H); ^{13}C NMR 171.07, 138.15, 129.46, 128.86, 126.50,

79.26, 78.07, 51.46, 44.53, 41.97, 35.05, 27.98, 26.49, 23.98, 22.12, 21.01, 18.42.

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(11) ***Synthesis of N-Boc-Perhydro-oxazin-4-ones. General procedure:*** Perhydro-oxazinone (1 mmol) was dissolved in anhydrous CH_2Cl_2 (10 ml), NEt_3 (1 mmol), DMAP (cat) and di-*tert*-butyldicarbonate were added. The mixture was stirred at r.t. (3h), the solvent was removed in vacuo and the residue filtered on a short silica gel column.
Synthesis of 3,3-dialkyl-β-hydroxy acids. General Procedure: *N*-Boc derivative of perhydro-oxazinone (1 mmol) was dissolved in a 1/1 solution of EtOH/H_2O. LiOH (5 mmol) was added and the mixture stirred at r.t. until t.l.c. spot test showed the disappearance of the starting material (3 hrs) The solution was concentrated at half the starting volume, the crude mixture was extracted with ethyl acetate and the aqueous layers made acidic by HCl 1N. Work-up by ethyl acetate and removal of the solvent yielded the β-hydroxy acid in almost quantitative yields. Any attempt to hydrolyze the unprotected perydro-oxazinone, so far, failed.

(12) The reported structures have been determined by NOE experiments irradiating the methyl group.

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