chlorotrimethylsilane, the corresponding organotrimethylsilane compound of the Grignard compound was obtained, which could be identified and quantified by GC/MS coupling (Table 2, entry 1).

Received July 6, 2000 [Z15395]

[1] a) L. E. Aleandri, B. Bogdanović, P. Bons, C. Dürr, A. Gaidies, T. Hartwig, S. C. Huckett, M. Lagarden, U. Wilczok, *Chem. Mater.* **1995**, *7*, 1153 – 1170; b) L. E. Aleandri, B. Bogdanović, C. Dürr, D. J. Jones, J. Rozière, U. Wilczok, *Adv. Mater.* **1996**, *8*, 600 – 604; c) L. E. Aleandri, B. Bogdanović, C. Dürr, S. C. Huckett, D. J. Jones, U. Kolb, M. Lagarden, J. Rozière, U. Wilczok, *Chem. Eur. J.* **1997**, *3*, 1710 – 1718; d) B. Bogdanović, W. Leitner, C. Six, U. Wilczok, K. Wittmann, *Angew. Chem.* **1997**, *109*, 518 – 520; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 502 – 504; e) G. Siedlaczek, M. Schwickardi, U. Kolb, B. Bogdanović, D. G. Blackmond, *Catal. Lett.* **1998**, *55*, 67 – 72.

[2] a) B. Bogdanović, M. Schwickardi (Studiengesellschaft Kohle mbH), PCT-WO 98/02443; b) B. Bogdanović, M. Schwickardi (Studiengesellschaft Kohle mbH), PCT-WO 99/33844.

[3] According to the literature **1** is generated from 1-chloronaphthaline and Mg turnings in boiling THF in 40% yield (6 h)[4] and by the entrainment method [5] in boiling diethyl ether in 66% yield (12 h).

[4] H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, R. Cserr, *J. Org. Chem.* **1957**, *22*, 1202 – 1206.

[5] D. A. Pearson, D. Cowan, J. D. Becker, *J. Org. Chem.* **1959**, *24*, 504 – 509.

[6] Grignard reactions, which proceed without a catalyst but first start after a long induction period can be initiated with this catalyst system.

[7] We thank the firm Bayer AG, Leverkusen, for providing a sample of **4a**.

[8] Patent registered.

[9] The rest is most likely to be the dimerization product $C_{14}H_{30}$.

[10] In light of EXAFS investigations (EXAFS = extended x-ray absorption fine structure), particularly of "$[Pt(MgCl)_2]$",[1c] we assume that the empirical formula $[M(MgCl)_m]_p(thf)_x$ ($m = 1,2,3$; $p \geq 2$) refers to the metal clusters M_p that are bound directly to the ligands MgCl(thf). The simplified form, such as "$[Fe(MgCl)_2]$" etc. denotes a fragment $1/p$ of this sort of cluster.

[11] C. Elschenbroich, A. Salzer, *Organometallchemie*, Teubner, Stuttgart, **1968**, p. 28.

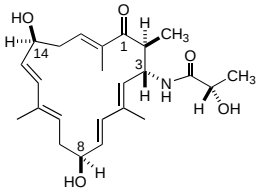
[12] Y. Gao, F. Sato, *J. Chem. Soc. Chem. Commun.* **1995**, 659 – 660.

[13] V. V. Grushin, H. Alper in *Activation of Unreactive Bonds and Organic Synthesis* (Ed.: S. Murai), Springer, Berlin, **1999**, p. 194.

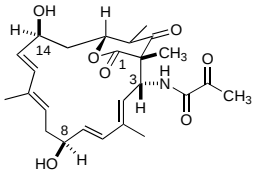
Total Synthesis of Lankacyclinol**

David R. Williams,* Guillermo S. Cortez, Stéphane L. Bogen, and Christian M. Rojas

The lankacidins are a family of structurally unique antibiotics isolated from the fermentation broths of *Streptomyces griseofuscus*, *S. violaceoniger*, and *S. rochei var.*[1] These metabolites show strong antitumor activity against L1210 leukemia, B16 melanoma, and solid lymphosarcoma cells.[2] Lankacyclinol (**1**), which is also identified as T-2636 G,[3] is a rare example of a seventeen-membered carbocycle, and incorporates two independent pentadienyl alcohol systems as well as a novel β-amido ketone moiety. The assignments of relative



Lankacyclinol **1**

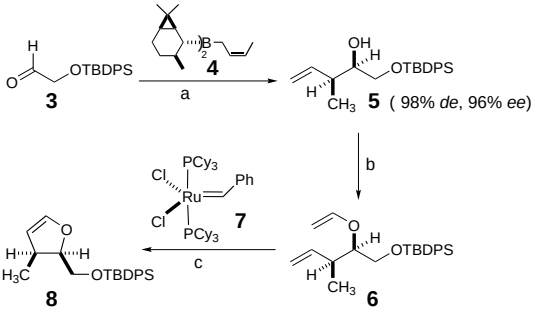


Lankacidin C **2**

stereochemistry at C3, C8, and C14, and the absolute configuration of **1** have been considered by comparison with lankacidin C (**2**) which was unambiguously characterized by X-ray crystallography.[4] Indeed, biosynthesis studies have suggested that enzymatic reduction of the 2′-oxopropionamide of **2** followed by base-induced decarboxylation provides lankacyclinol.[5]

However, the asymmetry at C2 of **1** has remained undefined in spite of substantial advancements leading to the synthesis of **2** by Kende and co-workers.[6] Our recent studies, stemming from 4,5-dihydrofurans, of tandem acyl nitrene insertions and Wittig reactions have demonstrated a stereocontrolled route to unique β-amido esters.[7] These results have provided the opportunity to address the challenges inherent in a proposed synthesis of **1**, particularly with regard to serious issues of acid and base instability and stereochemical concerns. In this communication, we describe the first enantioselective synthesis of (−)-lankacyclinol by a convergent pathway which establishes the relative and absolute configuration as illustrated in **1**.

An enantiocontrolled preparation of the C1 – C6 fragment was developed, which utilized *cis*-disubstituted dihydrofuran **8** and incorporated a ring-closing metathesis (RCM) strategy (Scheme 1). Addition of the (*Z*)-crotyl-di-(2-*iso*caranyl)borane **4**, as described by Brown and co-workers,[8] to aldehyde **3** gave the *syn*-homoallylic alcohol **5** as a single diastereomer.[9] Transetherification to afford the vinyl ether **6** was induced by treatment with ethyl vinyl ether in the presence of small amounts of mercuric trifluoroacetate.[10] Cyclization with the RCM protocol using the ruthenium Grubbs' catalyst **7**[11]



Scheme 1. a) **4**, $BF_3 \cdot Et_2O$, THF, −78 °C, 62%; b) $Hg(O_2CCF_3)_2$, ethyl vinyl ether, Et_3N, reflux, 60%; c) **7**, CH_2Cl_2, reflux, 48%. TBDPS = *tert*-butyldiphenylsilyl, Cy = cyclohexyl.

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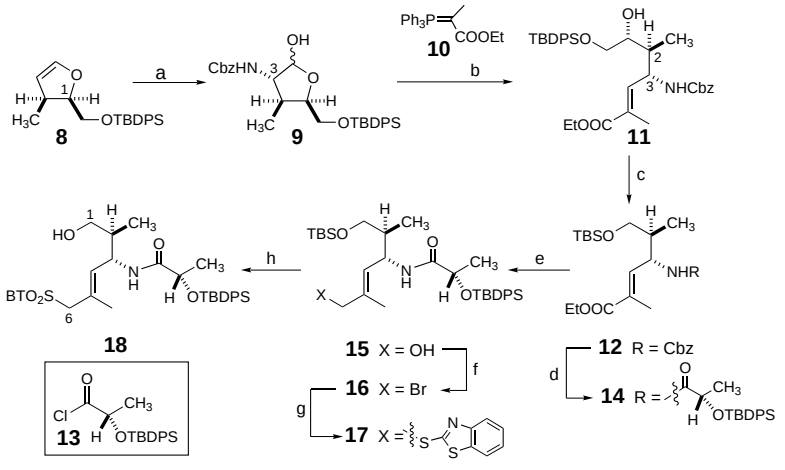
[**] Generous financial support for this research was provided by the National Institutes of Health (Award no.: GM41560). Additionally, a National Institutes of Health Minority Predoctoral Fellowship (Award no.: GM18547) to G.S.C. is gratefully acknowledged. We also wish to thank Dr. Tsuneaki Hida and Dr. Yoshio Kozai, Takeda Chemical Ltd. (Japan), for providing us with an authentic sample of lankacyclinol as well as copies of the original ^{1}H NMR spectrum.

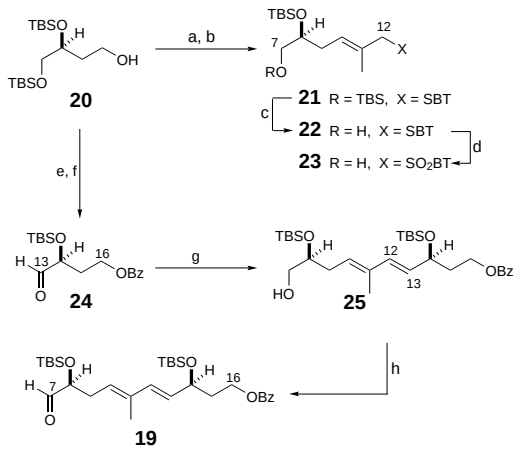
cleanly gave the 4,5-dihydrofuran **8** as a single product, which proved to be identical to material prepared from D-glutamic acid by an alternative route.[12, 13]

Introduction of the C3-amido appendage was undertaken by the C=C insertion of a reactive acyl nitrene with in situ reorganization to a *cis*-fused bicyclic oxazoline intermediate at room temperature.[7] As illustrated in Scheme 2, photolysis of benzyl azidoformate provided for facile insertion reactions with **8** to deliver the 2-amido furanose derivative **9** in 87% yield as the product of hydrolysis of the initially formed oxazoline. High diastereoselectivity (95:5) was imparted, to a large extent, by the steric consequences of the C1 substituent in **8**.[14] The lactol permitted direct elongation of the carbon chain by Wittig condensation with stabilized ylide **10** producing the *E* isomer of unsaturated ester **11** as a single diastereomer after flash chromatography. Standard conditions for the deprotection, oxidative cleavage, direct reduction, and protection as the Cbz carbamate provided **12**, which was utilized for introduction of the (*S*)-lactic acid residue. This task was accomplished by N-acylation of the *N*-lithium anion of **12** by acid chloride **13**[15] followed by immediate hydrogenolysis to afford the desired amide **14**. Chemoselective reduction of the α,β-unsaturated ester **14** was smoothly effected upon treatment with L-selectride to yield the primary allylic alcohol **15**. Incorporation of the benzothiazole functionality in **17** proceeded by displacement of the corresponding bromide **16**. Selective cleavage of the *tert*-butyldimethylsilyl ether followed by a sulfur oxidation[16] gave the fully elaborated C1 – C6 sulfone **18**.

In a highly convergent fashion, we constructed the C7 – C16 fragment by incorporating two units of L-malic acid to account for the asymmetry at C8 and C14, as shown in Scheme 3. Thus, the optically active primary alcohol **20**[17]



Scheme 2. a) Benzyl azidoformate, *hv*, 12 W low-pressure lamp, CH_2Cl_2, trace water, RT, 87%, (d.r. 95:5); b) **10**, $PhCH_3$, reflux, 77%; c) 1. TBAF, THF, 98%; 2. $NaIO_4$, THF/H_2O; 3. $NaBH_4$, CH_2Cl_2, MeOH; 4. TBSCl, imidazole, DMF, 95% (3 steps); d) 1. LiHMDS, THF, $-78\,^{\circ}C$, then acid chloride **13**, 92%; 2. Pd/$BaSO_4$, EtOAc, 80 psi (5.51×10^5 Pa) H_2, 80%; e) L-selectride, THF, $-78\,^{\circ}C \rightarrow$RT, 88%; f) 1. MsCl, 2,6-lutidine, CH_2Cl_2; 2. LiBr, THF, RT, 97%, (2 steps); g) *n*BuLi, 2-sulfanylbenzothiazole, THF, $-78\,^{\circ}C$, then add **16**, $-78\,^{\circ}C \rightarrow$RT, 97%; h) 1. PPTs (0.3 equiv), MeOH, cat. water, 85%; 2. $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (0.4 equiv), 50% H_2O_2 (8 equiv), EtOH, $0\,^{\circ}C \rightarrow$RT, 89%. Cbz = benzyloxycarbonyl, BT = 2-benzothiazole, TBAF = tetrabutylammonium fluoride, TBSCl = *tert*-butyldimethylsilyl chloride, DMF = dimethylformamide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, L-selectride = lithium tri-*sec*-butyl borohydride, MsCl = methanesulfonyl chloride, PPTs = pyridinium *p*-toluene sulfonate.

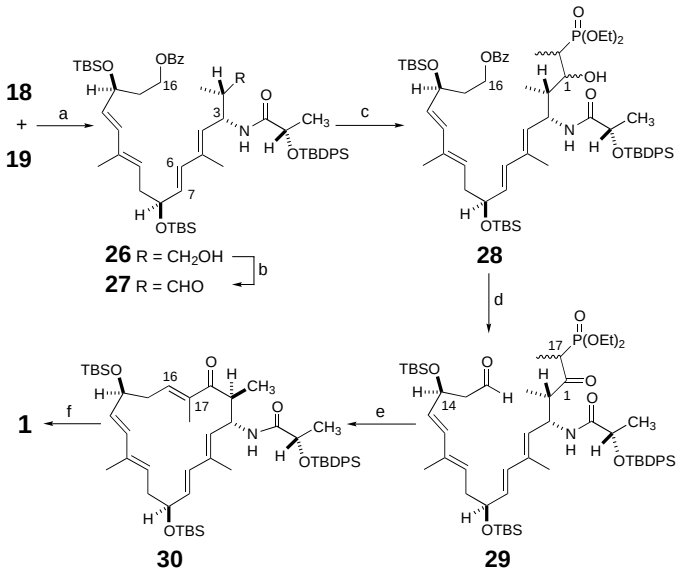


Scheme 3. a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-78\,^{\circ}C$, then add **10**, 88%; b) 1. DIBAL, CH_2Cl_2, $-78\,^{\circ}C$; 2. DEAD, Ph_3P, 2-sulfanylbenzothiazole, DMF, 96%, (2 steps); c) PPTs (0.3 equiv), 95% EtOH, 78%; d) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (0.4 equiv), 50% H_2O_2 (8 equiv), EtOH, $0\,^{\circ}C \rightarrow$RT, 91%; e) BzCl, Et_3N, CH_2Cl_2, 92%; f) 1. 48% HF, CH_3CN, 53%; 2. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-78\,^{\circ}C$, 91%; g) LDA (2.0 equiv) **23**, THF, $-78\,^{\circ}C$, 5 min, then add **24**, $-78\,^{\circ}C \rightarrow$RT, 3 h, 57%; h) Dess – Martin periodinane, $NaHCO_3$, CH_2Cl_2, 76%. DIBAL = diisobutylaluminum hydride, DEAD = diethyl azodicarboxylate, Bz = benzoyl, LDA = lithium diisopropylamide.

served a dual purpose. The oxidation and Wittig reaction starting from **20** were followed by hydride reduction and displacement to produce the benzothiazole sulfide **21**. In straightforward fashion, a three-step conversion of **20** led to aldehyde **24** without evidence of epimerization at C14 during the low-temperature Swern oxidation (91% yield).

A Julia olefination process was implemented for the coupling of fragments **23** and **24**.[18] Low-temperature deprotonation of sulfone **23** generated a reactive α-sulfonyl anion[19] which produced a single diastereomer **25** when the condensation reaction was allowed to warm to ambient temperature immediately after introduction of **24**. Flash chromatography purification afforded the *E*,*E* diene **25** in 57% yield, and Dess – Martin oxidation[20] gave aldehyde **19** with no evidence for epimerization at C8. However, the chemical instability of this system raised serious issues for devising our synthesis plan and manipulating advanced intermediates from this point forward.

The assembly of the functionalized C4 – C8 pentadienyl system of **1**, and closure of the large-ring carbocycle led to completion of the total synthesis as shown in Scheme 4. Expedient use of the modified Julia olefination[21] required formation of the dianion of sulfone **18** and condensation with optically pure aldehyde **19**. Notably, low-temperature deprotonation, to generate the α-sulfonyl carbanion of **18**, does not produce fragmentation by loss of the allylic C3-amido side chain, and undesired products due to N $\rightarrow$O acyl migration were not observed. In the event, the addition of aldehyde **19** led to the *E*,*E* diene **26** as a single isomer in 72% yield following flash



Scheme 4. a) LDA (2.05 equiv), **18**, THF, −78 °C (5 min), then add **19**, −78 °C →RT, 72 %; b) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 98 %; c) 1. LDA, ethyl diethylphosphonate, THF, −78 °C, 1 h; 2. $CeCl_3$, THF, −78 °C, 1 h, add **27**, −78 °C →RT, 61 %; d) 1. MeLi, Et_2O, −10 °C →RT, quench with $Na_2SO_4 \cdot 10\,H_2O$, 77 %; 2. Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 74 %; e) $Ba(OH)_2 \cdot 8\,H_2O$ (4×10^{-4} M), THF/H_2O (40/1), 59 %; f) TBAF (6.0 equiv), NH_4Cl (12.0 equiv), THF, 71 %.

chromatography. The Horner-Wadsworth-Emmons (HWE) process appeared to offer a mild technique for macrocyclization[22] and was pursued by the addition of the organocerium anion,[23] prepared from ethyl diethylphosphonate, to the sensitive aldehyde **27** to yield the β-hydroxyphosphonate **28** as a single diastereomer.[24] Our use of the more basic lithiophosphonate anion produced elimination of the C3-amido group to afford the corresponding conjugated triene from **27**. Nucleophilic cleavage of the C16 benzoate of **28** and a double oxidation using freshly prepared Dess–Martin reagent delivered the fragile ketoaldehyde **29** with undefined, albeit high, diastereomeric purity with regard to asymmetry at C17($\geq$98:2 d.r.).

Our initial attempts to perform an intramolecular HWE reaction using the usual Masamune–Roush conditions[25] led only to β-elimination of the C14-silyl group in **29**. Fortunately, our adaptation of the use of activated barium hydroxide hydrate, as described in a number of intermolecular HWE precedents[26] led, under high dilution conditions, to the formation of the seventeen-membered enone **30** in 59 % yield. A buffered, fluoride-induced deprotection produced lankacyclinol (**1**) as a white crystalline solid (mp 220 °C). Our synthetic sample was identical, in all respects, by direct comparison with a sample of naturally occurring **1**. Our efforts have established the assignment of relative stereochemistry and absolute configuration as shown in **1**.[27]

Received: August 8, 2000 [Z15600]

[1] a) E. Gaumann, R. Huter, W. Keller-Schierlein, L. Neipp, V. Prelog, H. Zahner, *Helv. Chim. Acta* **1960**, *43*, 601; b) S. Harada, T. Yamazaki, K. Hatano, K. Tsuchiya, T. Kishi, *J. Antibiot.* **1973**, *26*, 647; c) S. Harada, T. Kishi, *Chem. Pharm. Bull.* **1974**, *22*, 99.

[2] K. Ootsu, T. Matsumoto, H. Setsuo, T. Kishi, *Cancer Chemother. Rep. Part 1* **1975**, *59*, 919.

[3] S. Harada, *Chem. Pharm. Bull.* **1975**, *23*, 2201.

[4] a) K. Kamiya, S. Harada, Y. Wada, M. Nishikawa, T. Kishi, *Tetrahedron Lett.* **1969**, *27*, 2245; b) M. Uramoto, N. Otake, Y. Ogawa, H. Yonehara, *Tetrahedron Lett.* **1969**, *27*, 2249.

[5] S. Harada, S. Tanayama, T. Kishi, *J. Antibiot.* **1973**, *26*, 658.

[6] a) A. S. Kende, K. Koch, G. Dorey, I. Kaldor, K. Liu, *J. Am. Chem. Soc.* **1993**, *115*, 9842; b) A. S. Kende, K. Liu, I. Kaldor, G. Dorey, K. Koch, *J. Am. Chem. Soc.* **1995**, *117*, 8258.

[7] D. R. Williams, C. M. Rojas, S. L. Bogen, *J. Org. Chem.* **1999**, *64*, 736.

[8] a) H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919; b) U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 401.

[9] The corresponding *anti* isomer could not be detected by high-field ^{1}H NMR spectroscopy. The enantiomeric excess was estimated by ^{19}F and ^{1}H NMR data from the corresponding Mosher ester derivative.

[10] a) D. B. Tulshian, R. Tsang, B. Fraser-Reid, *J. Org. Chem.* **1984**, *49*, 2347; b) L. A. Paquette, T.-Z. Wang, C. M. G. Philippo, S. Wang, *J. Am. Chem. Soc.* **1994**, *116*, 3367.

[11] a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413; b) *Alkene Metathesis in Organic Synthesis* (Ed.: A. Fürstner), Springer, New York, **1998**.

[12] Optically active dihydrofuran **8** was prepared by reduction of (4*S*,5*R*)-4,5-dihydro-5-(*tert*-butyldiphenylsilyloxymethyl)-4-methyl-2(3*H*)-furanone from D-glutamic acid following the literature precedent for preparation of the enantiomeric butenolide: S. Hanessian, P. J. Murray, *J. Org. Chem.* **1987**, *52*, 1170.

[13] For examples of the RCM reaction of acyclic vinyl ethers to produce glycals, see: a) C. F. Sturino, J. C. Y. Wong, *Tetrahedron Lett.* **1998**, *39*, 9623; b) J. D. Rainier, S. P. Allwein, *J. Org. Chem.* **1998**, *63*, 5310.

[14] The diastereoselectivity was determined by mild oxidation to the corresponding lactone of **9**, and subsequent integrations of proton NMR signals for the C3 and C4 hydrogens.

[15] (*S*)-2-(*tert*-Butyldiphenylsilyloxy)-propionyl chloride (**13**) was prepared from (*S*)-ethyl lactate as follows: a) TBDPSCl, imidazole, DMF; b) LiOH, THF/H_2O; c) $(COCl)_2$, DMF, CH_2Cl_2 (50 %, 3 steps).

[16] H. S. Schultz, H. B. Freyermuth, S. R. Buc, *J. Org. Chem.* **1963**, *28*, 1140.

[17] a) A. Pommier, J.-M. Pons, P. J. Kocienski, *J. Org. Chem.* **1995**, *60*, 7334; b) S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, T. Moriwake, *Chem. Lett.* **1984**, 1389.

[18] a) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175; b) J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne, O. Ruel, *Bull. Chem. Soc. Fr.* **1993**, *130*, 856.

[19] For the generation of related hydroxysulfone dianions, see: a) R. Tanikaga, K. Hosoya, K. Hamamura, A. Kaji, *Tetrahedron Lett.* **1987**, *28*, 3705; b) R. Tanikaga, K. Hosoya, A. Kaji, *Chem. Lett.* **1987**, 829.

[20] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.

[21] a) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26; b) R. Bellingham, K. Jarowicki, P. Kocienski, V. Martin, *Synthesis* **1996**, 285; c) P. J. Kocienski, B. Lythgoe, S. Ruston, *J. Chem. Soc. Perkin Trans. 1* **1978**, 829.

[22] a) W. S. Wadsworth, Jr., *Org. React.* **1977**, *25*, 73; b) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863.

[23] For a review on the use of organocerium reagents, see: H.-J. Liu, K.-S. Shia, X. Shang, B.-Y. Zhu, *Tetrahedron* **1999**, *55*, 3803, and references therein.

[24] Best results for this coupling were obtained when high-quality $CeCl_3$ (Aldrich, 99.9 %) was pulverized to a fine powder with the aid of a mortar and pestle, and activated by heating to 120 °C under full vacuum for 1 hour, followed by cooling to ambient temperature under an inert atmosphere. The resulting white solid was suspended in THF for 30 minutes at ambient temperature and then cooled to −78 °C prior to addition of the lithium anion. For our purposes, the relative stereochemistry at C17 and C1 of β-hydroxyphosphonate **28** was inconsequential. However, ^{1}H and ^{13}C NMR data clearly indicated a single pure compound.

[25] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183.

[26] For the use of barium hydroxide in intermolecular HWE reactions, see: a) I. Paterson, K.-S. Yeung, J. B. Smaill, *Synlett* **1993**, 774, and references therein; b) J. A. Lafontaine, D. P. Provencal, C. Gardelli, J. W. Leahy, *Tetrahedron Lett.* **1999**, *40*, 4145.

  1433-7851/00/3924-4614 $ 17.50+.50/0

[27] Lankacyclinol (**1**): $R_f = 0.25$ in acetone/benzene (1/1); 0.21 in methyl ethyl ketone/ethyl acetate (2/8); mp 220 °C (uncorrected); synthetic **1**: $[\alpha]_D^{25} -163°$ ($c = 0.3$, EtOH), natural **1**: $[\alpha]_D^{25} -165°$ ($c = 0.35$, EtOH); IR (EtOH) $\tilde{\nu}_{max}$ 3422, 3096, 2996, 1661, 1624, 1105, 1078 cm^{-1}; ^1H NMR (500 MHz, [d_6]acetone): $\delta = 7.18$ (d, $J = 9.5$ Hz, NH), 6.56 (t, $J = 7.8$ Hz, 1H), 5.98 (d, $J = 15.6$ Hz, 1H), 5.70 (d, $J = 15.9$ Hz, 1H), 5.38 (dd, $J = 15.6$, 7.87 Hz, 1H), 5.32 (dd, $J = 15.9$, 7.87 Hz, 1H), 5.22–5.18 (m, 2H), 5.05 (q, $J = 9.9$ Hz, 1H), 4.28–4.20 (m, 1H), 4.10–4.00 (m, 3H), 3.66–3.60 (m, 1H), 2.60–2.54 (m, 2H), 2.42–2.36 (m, 1H), 2.28–2.19 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.52 (s, 3H), 1.29 (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, [d_6]acetone): $\delta = 203.2$, 174.64, 139.13, 137.88, 136.29, 135.73, 134.73, 131.76, 131.72, 130.04, 129.07, 74.48, 72.65, 68.97, 49.67, 43.79, 42.44, 38.54, 37.42, 21.74, 16.16, 13.23, 12.66, 12.55; MS (DCI/CH_4), m/z (%) 418 (4) [M^+], 400 (6) [$M^+ - H_2O$]; HR-MS (DCI/CH_4): calcd for $C_{24}H_{36}NO_5$ [MH^+]: 418.2593, found: 418.2573.

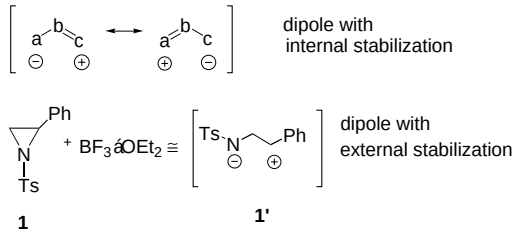
Phenylaziridine as a Masked 1,3 Dipole in Reactions with Nonactivated Alkenes**

Ioana Ungureanu, Philippe Klotz, and André Mann*

In memory of Toshiro Ibuka

Aziridines are known to react with a wide variety of nucleophiles, and their ability to undergo regioselective ring-opening reactions contributes largely to their synthetic value.[1] In our previous work, we disclosed a new type of reactivity for phenylaziridine **1**, a formal [3+2] dipolar cycloaddition on *activated* double bonds (Ts = tosyl = *p*-toluenesulfonyl). Phenylaziridine **1** reacts with allylsilanes[2] or dihydropyran (DHP)[3] in the presence of a Lewis acid to produce highly substituted pyrrolidines. This type of reactivity for aziridines has been noticed before, but has never been systematically investigated.[4]

We concluded that in the presence of $BF_3 \cdot Et_2O$ at −78 °C, **1** reacts via **1′**, a rather uncommon 1,3 dipole (Scheme 1). The two charges of **1′** are isolated by an sp^3-hybridized carbon atom, and therefore, according to Huisgen, an internal stabilization by delocalization, as found in classical 1,3 dipoles,

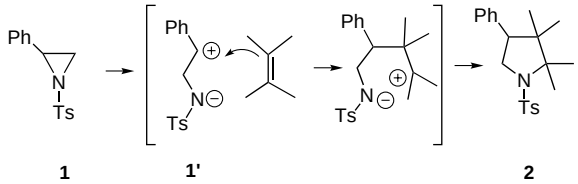


Scheme 1. Possible modes of dipole stabilization.[5]

is not possible.[5] In contrast, **1′** is stabilized externally by the double contributions of the aromatic ring and the arylsulfonyl group. Thus, following the Huisgen classification **1′** can be considered as a zwitterionic 1,3 dipole.[5] More interestingly, **1′** is electron deficient and should thus react with electron-rich partners. Therefore we wondered if **1** reacts with *nonactivated* olefinic double bonds.

Herein we present our results on the reactivity of **1** with alkenes. This new use of **1** as a 1,3-dipole precursor is an advance on our recent work,[3] and of importance, not only from its theoretical, but also from its preparative significance in providing direct access to substituted pyrrolidines.

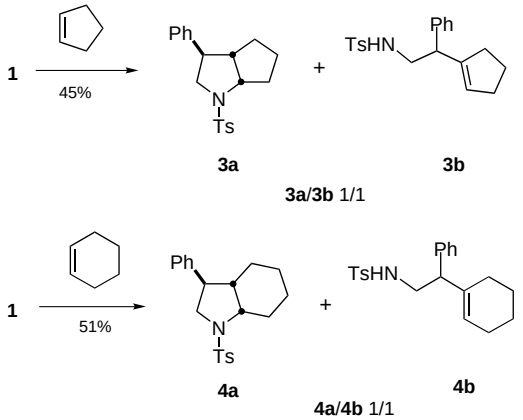
To avoid undesirable problems with regioselectivity we first considered a symmetrically substituted alkene.[6] Therefore we chose to react tetramethylethylene with **1** in the presence of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at −78 °C (the same experimental conditions were used for all reactions with **1**). A fast reaction took place and the only isolated product was the pyrrolidine **2** in 92% yield (Scheme 2).



Scheme 2. Reaction of **1** with tetramethylethylene.

This result shows that **1′** is electron deficient enough to react even with a *nonactivated* alkene. The dipole **1′** is produced at −78 °C, the olefinic π system attacks at the benzylic position giving rise to a stable tertiary carbocation, ready for a ring closure with the adjacent amide. This process constitutes a formal [3+2] cycloaddition that is useful for the synthesis of 2,2,3,3-tetrasubstituted pyrrolidines.

To explore the generality of this heterocyclization, we examined the reactivity of **1** towards cyclopentene and cyclohexene. We identified for each alkene a pair of product compounds **3a**/**3b** and **4a**/**4b**, formed in a 1/1 ratio in a total yield around 50% (Scheme 3). The bicyclic adducts **3a** and **4a** are isolated as single diastereomers, and their relative



Scheme 3. Reaction of **1** with cycloalkenes.

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[**] We thank Professor C. G. Wermuth for stimulating discussions.

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