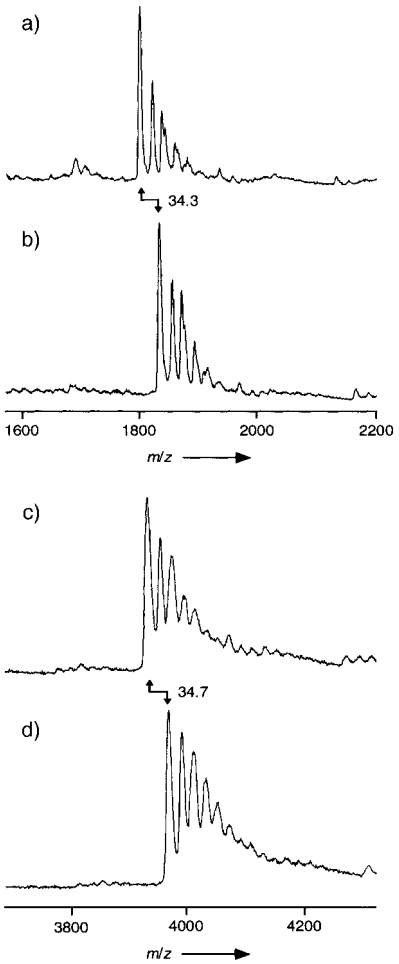


Figure 3. MALDI-TOF MS analysis of: a) d(GCTAGC); b) d(GCTgAGC); c) d(ACGCGATACGCCA); and d) d(ACGCGATgACGCCA).

[5] M. J. Lustig, J. Cadet, R. J. Boorstein, G. W. Teebor, *Nucleic Acids Res.* **1992**, *20*, 4839 – 4845.

[6] a) R. C. Hayes, L. A. Petrullo, H. Huang, S. S. Wallace, J. E. LeClerc, *J. Mol. Biol.* **1988**, *201*, 239 – 246; b) A. K. Basu, E. L. Loechler, S. A. Leadon, J. M. Essigmann, *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 7677 – 7681.

[7] a) H. Ide, Y. W. Kow, S. S. Wallace, *Nucleic Acids Res.* **1985**, *13*, 8035 – 8052; b) J. M. Clark, G. P. Beardsley, *Nucleic Acids Res.* **1986**, *14*, 737 – 749; c) R. C. Hayes, J. E. LeClerc, *Nucleic Acids Res.* **1986**, *14*, 1045 – 1061; d) J. M. McNulty, B. Jerkovic, P. H. Bolton, A. K. Basu, *Chem. Res. Toxicol.* **1998**, *11*, 666 – 673.

[8] a) B. Demple, S. Linn, *Nature* **1980**, *287*, 203 – 208; b) M. Dizdaroglu, J. Laval, S. Boiteux, *Biochemistry* **1993**, *32*, 12105 – 12111; c) S. Ikeda, T. Biswas, R. Roy, T. Izumi, I. Boldogh, A. Kurosky, A. H. Sarker, S. Seki, S. Mitra, *J. Biol. Chem.* **1998**, *273*, 21585 – 21593.

[9] R. J. Melamede, Z. Hatahet, Y. W. Kow, H. Ide, S. S. Wallace, *Biochemistry* **1994**, *33*, 1255 – 1264.

[10] J. T. Reardon, T. Bessho, H. C. Kung, P. H. Bolton, A. Sancar, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 9463 – 9468.

[11] C. D'Ham, A. Romieu, M. Jaquinod, D. Gasparutto, J. Cadet, *Biochemistry* **1999**, *38*, 3335 – 3344.

[12] J. Y. Kao, I. Goljer, T. A. Phan, P. H. Bolton, *J. Biol. Chem.* **1993**, *268*, 17787 – 17793.

[13] N. D. Sinha, P. Davis, N. Usman, J. Pérez, R. Hodge, J. Kremsky, R. Casale, *Biochimie* **1993**, *75*, 13 – 23.

[14] N. Usman, K. K. Ogilvie, M.-Y. Jiang, R. J. Cedergren, *J. Am. Chem. Soc.* **1987**, *109*, 7845 – 7854.

[15] J. S. Baran, *J. Org. Chem.* **1960**, *25*, 257.

[16] M. R. Barvian, M. M. Greenberg, *J. Org. Chem.* **1993**, *58*, 6151 – 6154.

[17] W. H. A. Kuijpers, J. Huskens, L. H. Koole, C. A. A. van Boeckel, *Nucleic Acids Res.* **1990**, *18*, 5197 – 5205.

[18] N. D. Sinha, J. Biernat, J. McManus, H. Köster, *Nucleic Acids Res.* **1984**, *12*, 4539 – 4557.

[19] J. Stawinski, R. Strömberg, M. Thelin, E. Westman, *Nucleic Acids Res.* **1988**, *16*, 9285 – 9298.

[20] a) S. Iwai, M. Shimizu, H. Kamiya, E. Ohtsuka, *J. Am. Chem. Soc.* **1996**, *118*, 7642 – 7643; b) T. Mizukoshi, K. Hitomi, T. Todo, S. Iwai, *J. Am. Chem. Soc.* **1998**, *120*, 10634 – 10642.

[21] a) Y. Fujiwara, S. Iwai, *Biochemistry* **1997**, *36*, 1544 – 1550; b) K. Hitomi, S.-T. Kim, S. Iwai, N. Harima, E. Otoshi, M. Ikenaga, T. Todo, *J. Biol. Chem.* **1997**, *272*, 32591 – 32598; c) H. Kamiya, S. Iwai, H. Kasai, *Nucleic Acids Res.* **1998**, *26*, 2611 – 2617; d) K. Sugasawa, J. M. Y. Ng, C. Masutani, S. Iwai, P. J. van der Spek, A. P. M. Eker, F. Hanaoka, D. Bootsma, J. H. J. Hoeijmakers, *Mol. Cell* **1998**, *2*, 223 – 232; e) Y. Fujiwara, C. Masutani, T. Mizukoshi, J. Kondo, F. Hanaoka, S. Iwai, *J. Biol. Chem.* **1999**, *274*, 20027 – 20033.

[22] J. Butenandt, L. T. Burgdorf, T. Carell, *Synthesis* **1999**, 1085 – 1105.

A Concise Stereoselective Route to the Pentacyclic Frameworks of Arisugacin A and Territrem B**

Luke R. Zehnder, Richard P. Hsung,* Jiashi Wang, and Geoffrey M. Golding

Arisugacin A (**1a**, Scheme 1) was first isolated from *Penicillium* sp. Fo-4259 as a potent and selective inhibitor of acetylcholinesterase (AChE) with an IC_{50} value of 1 nM.[1] Because of the potential therapeutic value of **1a** in the treatment of Alzheimer's disease,[2] and the structural similarity of **1a** to important natural products such as territrems (for example, territrem B (**2**))[3] and pyripyropenes,[4] we have been exploring a number of different synthetic routes that may be suitable for an efficient and stereoselective synthesis of arisugacins or territrems.[5, 6] Our recent work involving a formal [3+3] cycloaddition reaction using α,β-unsaturated iminiums and diketo systems[7–9] allowed us to envision a highly concise entry to these natural products. We report here our success in using a stereoselective variant of this formal cycloaddition reaction to construct the pentacyclic frameworks of arisugacin A (**1a**) and territrem B (**2**).

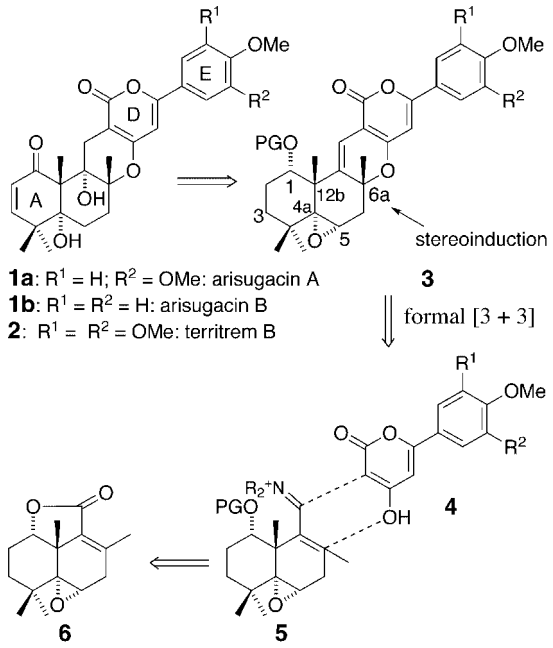
An advanced pentacyclic intermediate such as **3** that is suitable for the syntheses of arisugacins and territrems can be obtained readily by a stereoselective formal [3+3] cycloaddition reaction using the 4-hydroxy-2-pyrone **4**[10] and α,β-unsaturated iminium **5** (Scheme 1). The critical stereoinduction to be achieved in this key reaction is the stereochemistry

[*] Prof. R. P. Hsung, L. R. Zehnder, J. Wang, G. M. Golding
Department of Chemistry
University of Minnesota
Minneapolis, MN 55455 (USA)
Fax: (+1) 612-626-7541
E-mail: hsung@chem.umn.edu

[**] This work was supported by the University of Minnesota.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/00/3921-3876 $ 17.50+.50/0

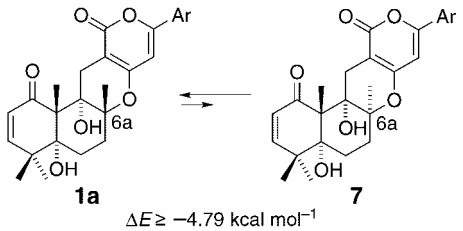


Scheme 1. PG = protecting group.

of the angular methyl group at C6a. The formation of iminium **5** from the epoxy lactone **6** may be envisioned and this should give the required stereochemistry at C12b and C4a in the AB ring.

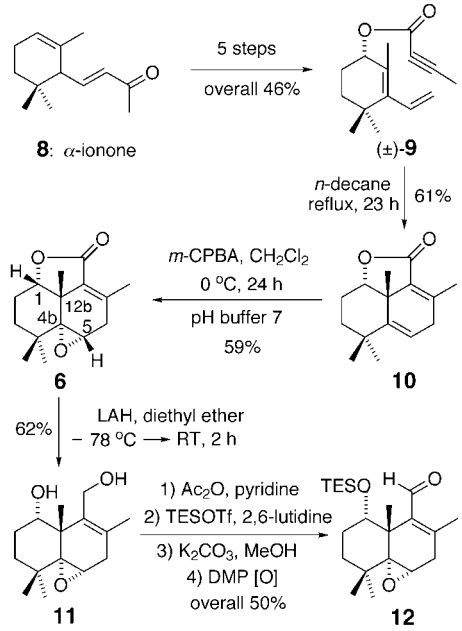
Although this proposed route appears to be feasible on the basis of the existing understanding of the key formal [3+3] cycloaddition,[6a, 9a] there are two major uncertainties that could cause this attempt to fail. First, we have demonstrated that α,β-unsaturated iminium groups containing steric encumbrance comparable to that in **5** can effectively shut down the reaction.[9a, 11] Second, and more significantly, there have been no successful stereoselective examples of this particular formal cycloaddition using chiral α,β-unsaturated iminium groups.[6a, 9a, 11] Hence, the ability to control the stereochemistry at C6a through this reaction was highly speculative.

Recent work, however, suggested that the 6π-electron electrocyclic ring closure, the third mechanistic step in these formal [3+3] cycloaddition reactions, is reversible, and leads to the thermodynamically more-stable isomer with high diastereoselectivity.[8] Our calculations (PM3 using the Spartan package) suggested that the diastereomer **7**, in which the angular methyl group at C6a is β (Scheme 2), is 4.79 kcal mol^{-1} more stable than the α-epimer. This result suggests that a favorable diastereoselective control could be achieved in a thermodynamic manner by using α,β-unsaturated iminium compounds such as **5**.



Scheme 2. Ar = 3,4-dimethoxyphenyl.

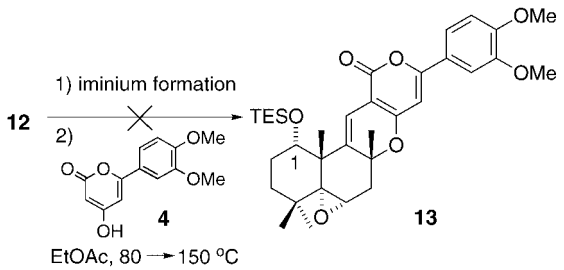
Encouraged by this calculation we pursued the synthesis of α,β-unsaturated aldehydes that would serve as precursors to **5**. The racemic ester **9** (Scheme 3) could be obtained readily in five steps from α-ionone (**8**) in 46% overall yield by a sequence previously used in the synthesis of forskolin.[12] A subsequent intramolecular Diels–Alder reaction of **9**[13] followed by epoxidation led to the α-epoxy lactone **6**[14] in



Scheme 3. *m*-CPBA = *meta*-chloroperbenzoic acid; LAH = lithium aluminum hydride; TESOTf = triethylsilyl trifluoromethanesulfonate; DMP[O] = Dess–Martin oxidation.

59% yield. The corresponding β-epoxy isomer was also isolated in 10–20% yield. The stereochemistry of **6** was assigned using global NOE experiments, and it was thereby established that the relative stereochemistry required at C4a and C12b for arisugacins and territrems was present. Compound **6** was reduced to the diol **11** in 62% yield using LAH, with the epoxide remaining unopened. Appropriate functional group manipulations provided the aldehyde **12** in 50% overall yield from **11** (see Supporting Information).

Under our standard conditions,[9a] as well as a under a variety of other conditions known to generate iminium groups, formal [3+3] cycloaddition reactions of **12** with the pyrone **4** failed to provide the desired pentacycle **13** (Scheme 4). This failure prompted us to speculate that the

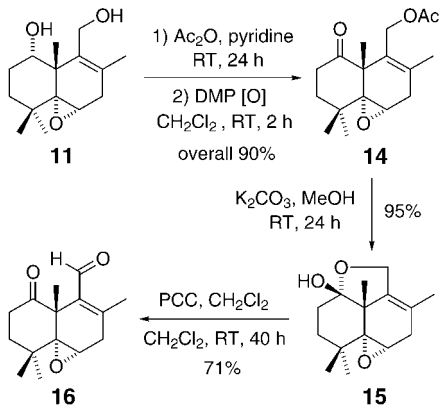


Scheme 4.

  1433-7851/00/3921-3877 $ 17.50+.50/0

aldehyde **12** may be too sterically hindered, thereby effectively shutting down the cycloaddition reaction pathway.[9] Inspection of molecular models revealed that this steric congestion could be alleviated if the C1 carbon atom was sp^2 hybridized.

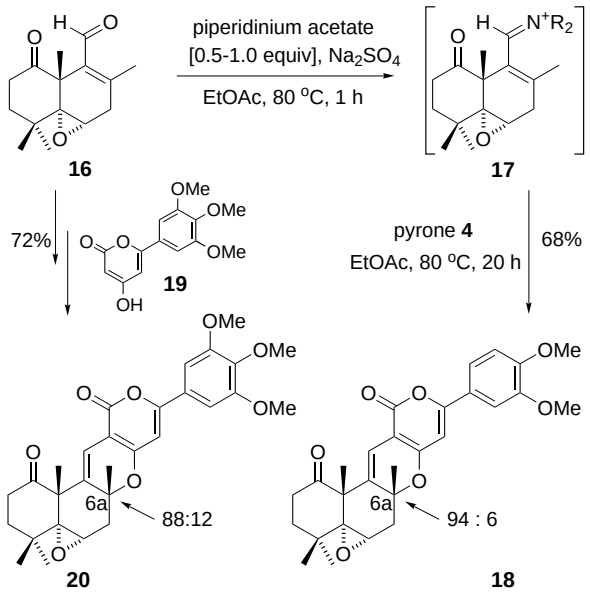
Acetylation of the diol **11**, followed by Dess–Martin oxidation, afforded the ketone **14** in 90% overall yield (Scheme 5). Deacetylation of **14** led to the formation of the lactol **15**, and only oxidation with PCC was successful in giving



Scheme 5. PCC = pyridinium chlorochromate.

the ketoaldehyde **16** (71% yield, 75% conversion). The ketoaldehyde **16** proved to be suitable for the construction of pentacycles. The iminium intermediate **17** was generated from **16** using 0.5–1.0 equivalents of piperidinium acetate in the presence of Na_2SO_4 at 80 °C for 1 h (Scheme 6).[15] A subsequent formal [3+3] cycloaddition reaction with pyrone **4** in EtOAc at 80 °C for 20 h enabled the pentacycle **18** to be isolated in 68% yield with a diastereomeric ratio of 94:6.

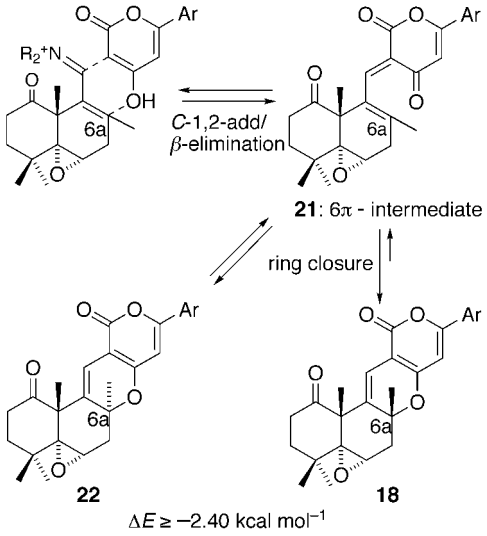
The angular methyl group at C6a was established as β for the major isomer of **18** and α for the minor isomer by using NOE experiments. The pentacycle **18** should prove to be



Scheme 6.

useful for the synthesis of arisugacin A (**1a**). By using 6-(3,4,5-trimethoxyphenyl)-4-hydroxy-2-pyrone (**19**) under the same reaction conditions the pentacycle **20** was obtained in 72% yield with a diastereomeric ratio of 88:12, with the β-epimer again being the major product. Compound **20** contains the desired E-ring necessary for the synthesis of territrem B (**2**).

The high diastereoselectivity obtained in these reactions here can be explained as a result of the reversible 6π-electron electrocyclic ring closure[7, 16] via the 6π intermediate (**21** in Scheme 7), which leads to the thermodynamically more stable isomer **18**. Our PM3 calculations again support that compound **18** is more stable than **22** by about 2.40 kcal mol^{-1}.



Scheme 7. Ar = 3,4-dimethoxyphenyl.

We have described here a concise route to the pentacyclic frameworks of arisugacin A and territrem B using a stereoselective formal [3+3] cycloaddition reaction. Efforts to complete the total syntheses of arisugacins and territrems using this synthetic approach are still underway.

Received: April 27, 2000 [Z15050]

[1] K. Otoguro, F. Kuno, S. Õmura, *Pharmacol. Ther.* **1997**, *76*, 45.

[2] V. John, I. Lieberburg, E. D. Thorsett, *Annu. Rep. Med. Chem.* **1993**, *28*, 197.

[3] a) K. H. Ling, C.-K. Yang, F.-T. Peng, *Appl. Environ. Micobiol.* **1979**, *37*, 355; b) T. H. Hseu, C.-K. Yang, K. H. Ling, C. J. Wang, C. P. Tang, *Cryst. Struct. Commun.* **1982**, *11*, 199; c) S.-S. Lee, F.-C. Peng, C.-M. Chiou, K. H. Ling, *J. Nat. Prod.* **1992**, *55*, 251.

[4] a) H. Tomoda, N. Tabata, D. J. Yang, I. Namatame, H. Tanaka, S. Õmura, T. Kaneko, *J. Antibiotics* **1996**, *49*, 292; b) A. B. Smith III, T. Kinsho, T. Sunazuka, S. Õmura, *Tetrahedron Lett.* **1996**, 6461; c) T. Nagamitsu, T. Sunazuka, R. Obata, H. Tomoda, H. Tanaka, Y. Harigaya, S. Õmura, A. B. Smith III, *J. Org. Chem.* **1995**, *60*, 8126; d) K. A. Parker, L. Resnick, *J. Org. Chem.* **1995**, *60*, 5726.

[5] a) R. P. Hsung, *J. Org. Chem.* **1997**, *62*, 7904; b) K. G. Granum, G. Merkel, J. A. Mulder, S. A. Debbins, R. P. Hsung, *Tetrahedron Lett.* **1998**, 9597.

[6] For other related studies, see a) D. H. Hua, Y. Chen, H.-S. Sin, M. J. Maroto, P. D. Robinson, S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freeman, J.-P. Perchellet, P. K. Chiang, *J. Org. Chem.* **1997**, *62*, 6888; b) R. Obata, T. Sunazuka, Z. Tian, H. Tomoda, Y. Harigaya, S. Õmura, A. B. Smith III, *Chemistry Lett.* **1997**, 935.

  1433-7851/00/3921-3878 $ 17.50+.50/0

[7] a) H. M. Sklenicka, R. P. Hsung, L.-L. Wei, M. J. McLaughlin, A. I. Gerasyuto, S. J. Degen, J. A. Mulder, *Organic Lett.* **2000**, *2*, 1161; b) R. P. Hsung, L.-L. Wei, H. M. Sklenicka, H. C. Shen, M. J. McLaughlin, L. R. Zehnder in *Advances in Cycloaddition* (Ed.: M. Harmata), JAI, Greenwich, **2000**, in press.
[8] R. P. Hsung, L.-L. Wei, H. H. Sklenicka, C. J. Douglas, M. J. McLaughlin, J. A. Mulder, L. J. Yao, *Organic Lett.* **1999**, *1*, 509.
[9] a) R. P. Hsung, H. C. Shen, C. J. Douglas, C. D. Morgan, S. J. Degen, L. J. Yao, *J. Org. Chem.* **1999**, *64*, 690; b) L. R. Zehnder, J. W. Dahl, R. P. Hsung, *Tetrahedron Lett*. **2000**, 1901.
[10] C. J. Douglas, H. M. Sklenicka, H. C. Shen, G. M. Golding, D. S. Mathias, S. J. Degen, C. D. Morgan, R. A. Shih, K. L. Mueller, L. H. Seurer, E. W. Johnson, R. P. Hsung, *Tetrahedron* **1999**, *55*, 13683.
[11] M. Jonassohn, O. Sterner, H. Anke, *Tetrahedron* **1996**, *52*, 1473.
[12] a) K. C. Nicolaou, W. S. Li, *J. Chem. Soc. Chem. Commun.* **1985**, 421; For related approaches, see b) E. J. Corey, P. D. S. Jardine, J. C. Rohloff, *J. Am. Chem. Soc.* **1988**, *110*, 3672; c) F. E. Ziegler, B. H. Jaynes, M. T. Saindane, *J. Am. Chem. Soc.* **1987**, *109*, 8115; d) P. R. Jenkins, K. A. Menear, P. Barraclough, M. S. Nobbs, *J. Chem. Soc. Chem. Commun.* **1984**, 1423.
[13] B. Delpech, D. Calvo, R. Lett, *Tetrahedron Lett*. **1996**, 1015.
[14] All new compounds are characterized by ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy, as well as mass spectrometry.
[15] a) L. E. Overman, M. H. Rabinowitz, *J. Org. Chem.* **1993**, *58*, 3235; b) L. E. Overman, M. H. Rabinowitz, P. A. Renhowe, *J. Am. Chem. Soc.* **1995**, *117*, 2657.
[16] For leading references on electrocyclic ring closures involving 1-oxa- or 1-azatrienes, see a) T. Kametani, M. Kajiwara, K. Fukumoto, *Tetrahedron* **1974**, *30*, 1053; b) K. Shishido, M. Ito, S.-I. Shimada, K. Fukumoto, T. Kametani, *Chem. Lett.* **1984**, 1943; c) D. F. Maynard, W. H. Okamura, *J. Org. Chem* **1995**, *60*, 1763; d) W. H. Okamura, A. R. de Lera, W. Reischl, *J. Am. Chem. Soc.* **1988**, *110*, 4462.

Formation of the Unprecedented Trilithio-Capped Heteroadamantanyl Iminoalane Anion $[(HAl)_4(NPh)_6\{Li(OEt_2)\}_3]^-$: An Open Cage Derived from a Rhombododecahedron**

Kenneth W. Henderson,* Alan R. Kennedy, Arlene E. McKeown, and Robert E. Mulvey

There is a great deal of current interest in the preparation of organometallic compounds containing combinations of p-block elements due to their uses in the electronics industry,[1] in catalysis,[2] and in the search for new types of π bonding.[3] As a result, a wide variety of heterodimetallic species that adopt polyhedral cage frameworks have been characterized, and structural patterns within their mixed-metal cores are now emerging. A notable example exists for the isovalent series of compounds with general formulas $M_4E_6Li_4$ (where M = AlH, E = AsSi*i*Pr$_3$; M = AlMe or Sn, E = PC_6H_{11})[4] or $M_2E_6Li_6$ (where M = Sb, E = NCH_2CH_2Ph, NC_6H_{11}, N*t*Bu, $NC_6H_3(OMe)_2$, or PC_6H_{11};[5] M = Ge*t*Bu, E = AsSi*i*Pr$_3$;[6] M = SiR, E = NR′,[7] where R = H, R′ = Me$_3$Si; R = Me, *t*Bu or Ph, R′ = Me$_3$Si; R = Me or Ph, R′ = *t*Bu; R = Me or *t*Bu, R′ = Me; M = SiEt, E = PSi*i*Pr$_3$), which all adopt structures containing very similar 14-membered rhombodo-decahedral cage cores (Lewis base complexants within the compounds are ignored for simplicity). In contrast, we now report the synthesis of the novel, charge-separated complex **1**, which though isovalent with the above compounds adopts a unique molecular geometry.

$$[Li(OEt_2)_3]^+[(HAl)_4(NPh)_6\{Li(OEt_2)\}_3]^- \qquad \mathbf{1}$$

Complex **1** was originally prepared from the equimolar reaction between the primary amidolithium PhN(H)Li and the alane adduct $H_3Al\cdot N(Me)C_5H_8$ (where $N(Me)C_5H_8$ = 1-methyl-1,2,3,6-tetrahydropyridine)[8] in diethyl ether solution. However, measurement of H_2 evolution from the reaction has established that the ideal stoichiometry for the preparation of **1** is that shown in Equation (1). Crystallographic analysis of **1**

$$6\,PhN(H)Li + 4\,H_3Al\cdot N(Me)C_5H_8 \xrightarrow[-4\,MeNC_5H_8]{Et_2O} \mathbf{1} + 2\,LiH + 6\,H_2 \qquad (1)$$

revealed a remarkable structure consisting of a cage anion (**1a**; Figure 1) and a solvent-separated countercation, with no discernible close contacts between the two.[9]

Solution NMR data (^{27}Al and low-temperature ^{7}Li) appear to be consistent with the solid-state structure of **1**, indicating the presence of two distinct signals (apical/equatorial Al, and cation/anion Li). However, a full understanding of the

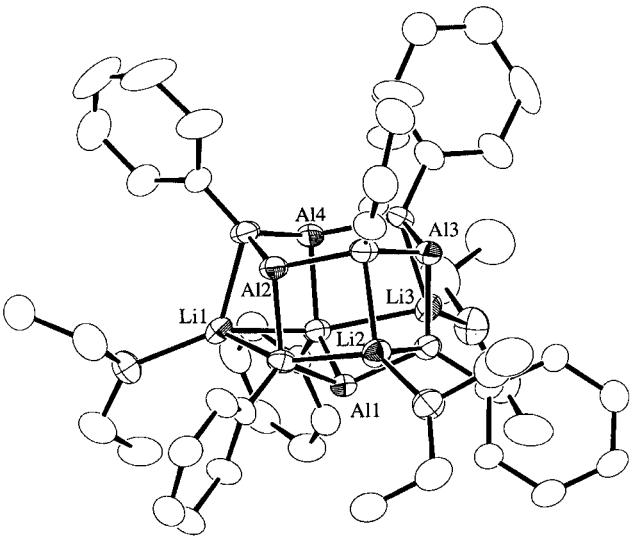


Figure 1. Molecular structure of **1a** with hydrogen atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Al1-N1 1.882(6), Al1-N3 1.901(7), Al1-N4 1.895(6), Al2-N1 1.914(6), Al2-N2 1.873(7), Al2-N5 1.881(7), Al3-N2 1.860(7), Al3-N3 1.918(6), Al3-N6 1.890(7), Al4-N4 1.924(6), Al4-N5 1.881(7), Al4-N6 1.868(7), Li1-O1 1.929(14), Li2-O2 1.950(14), Li3-O3 1.930(13), Li1-N1 2.205(15), Li1-N4 2.227(15), Li1-N5 2.106(14), Li2-N1 2.218(15), Li2-N2 2.059(14), Li2-N3 2.227(15), Li3-N3 2.225(14), Li3-N4 2.221(14), Li3-N6 2.069(13); N-Li-N 84.97 (mean), N-Al1-N 104.17 (mean), N-Al2-N 105.40 (mean), N-Al3-N 105.40 (mean), N-Al4-N 105.73 (mean).

[*] Dr. K. W. Henderson, Dr. A. R. Kennedy, A. E. McKeown, Prof. R. E. Mulvey
Department of Pure and Applied Chemistry
University of Strathclyde
Glasgow, G1 1XL (UK)
Fax: (+44) 141-552-0876
E-mail: k.w.henderson@strath.ac.uk

[**] We thank the Royal Society for a University Research Fellowship (K.W.H.) and BP Amoco for funding (A.E.M.).