Pergamon

Tetrahedron Letters, Vol. 36, No. 48, pp. 8737-8740, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01898-0

ON THE FLEXIBILITY OF ALLYLIC AZIDES AS SYNTHETIC INTERMEDIATES

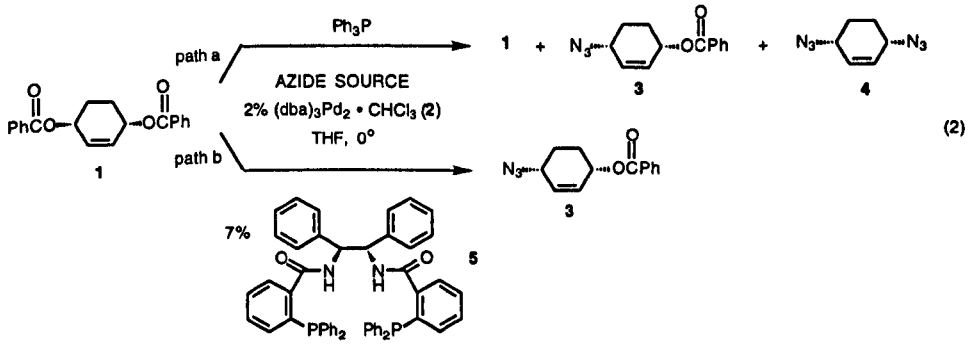
Barry M. Trost and Shon R. Pulley
Department of Chemistry
Stanford University
Stanford, CA 94305-5080

Summary: Asymmetric synthesis of an allylic azide combined with the facility of the [3.3]sigmatropic rearrangement provides a simple strategy for the synthesis of conduramine E.

The synthesis of allylic azides is complicated by their propensity to undergo [3.3]-sigmatropic rearrangements as shown in eq 1.[1] Previously, it has been noted that in the palladium catalyzed azidation of allylic esters, the product reflected the thermodynamic mixture of regioisomers.[2] The formation of such mixtures detracts from their utility in synthesis. In the optimum situation, both regioisomers would be available.

(1)

In conjunction with our interest in asymmetric syntheses of alkaloids, we initiated a study of the asymmetric azidation of diesters of meso-2-en-1,4-diols.[3] As a starting point, the reaction of the six membered ring dibenzoate **1** with trimethylsilyl azide in the presence of the palladium(0) source **2** and triphenylphosphine gave virtually the statistical 1:2:1 mixture of starting material: monoazide **3**:diazide **4** (eq 2, path a). In stark

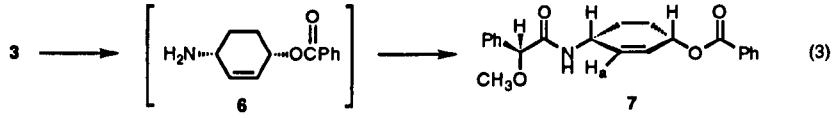


(2)

contrast to this result, use of the chiral ligand **5**[3] gave the alkylation product with a >17:1 ratio of **3**:**4** (eq 2, path b). This ratio was also dependent upon the alkylation conditions. For example, switching to sodium azide in aqueous THF under otherwise identical conditions with chiral ligand **5** gave a 6:1 ratio of monoazide **3** to diazide **4**. Thus, one benefit of the chiral ligand is to minimize the problem of polyalkylation. In neither case

was the product of [3.3]-sigmatropic rearrangement observed.

To determine the enantioselectivity of the reaction with the chiral ligand **5**, the azide was reduced with triphenylphosphine in THF followed by addition of water[5] to form the amine **6** which was directly acylated with (S)-O-methylmandelic acid and DCC (eq 3). The ^{1}H nmr spectrum of the resulting amide **7** showed signals for

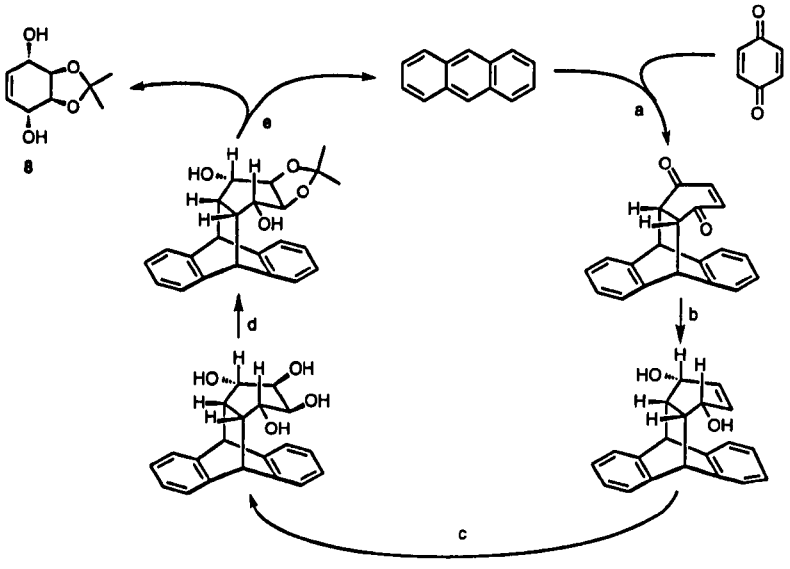


(3)

only one diastereomer, indicating a de of >95% for **7** and, consequently, an ee of >95% for **3**. This spectrum also allowed assignment of the absolute configuration as depicted (δ_{H_a} 5.82 for **7** vs δ 5.94 for the diastereomer).[6]

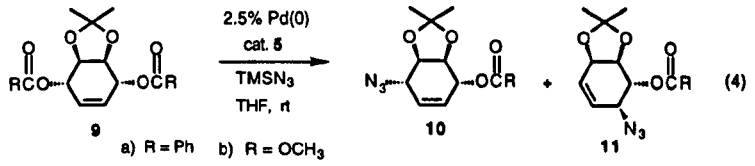
For the synthesis of some of the conduramines,[7,8] conduritol A acetonide (**8**) was prepared as shown in Scheme 1 using a modification of the method of Cambie et al.[9] This sequence transforms 1,4-benzoquinone

Scheme 1. Synthesis of Monoacetonide of Conduritol A (**8**)

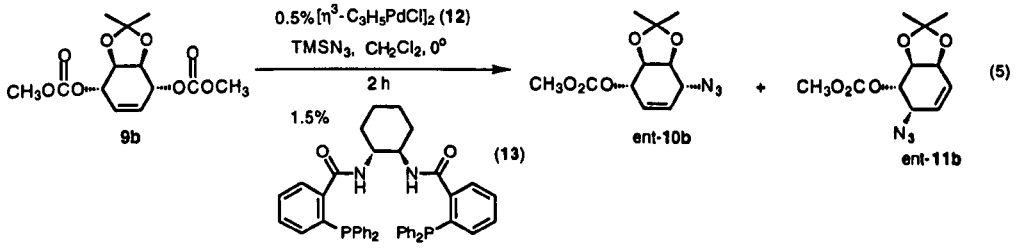


a) Xylene, reflux, 90%. b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_3OH, CH_2Cl_2, 94%. c) cat. OsO_4, NMO•$2H_2O$, C_5H_5N, t-C_4H_9OH, H_2O, reflux, 91%. d) CH_3COCH_3, $CH_3C(OCH_3)_2CH_3$, TsOH, 95%. e) FVT, 500°, 94%.

into the diol **8** with complete control of diastereoselectivity in 69% overall yield and permits recycling of anthracene. The dibenzoate **9a** differed in its behavior from the parent system **1** in that both regioisomeric azides **10a**[4] and **11a**[4] were produced with the same chiral catalyst (eq 4). Using **2** as the palladium(0) source gave a 2.5:1 ratio after 20 h (56% yield). With π-allylpalladium chloride dimer (**12**) as the palladium(0) source, the reaction proceeded more quickly to give a 51% yield after 8h at r.t. and a 3.4:1 ratio of the regioisomeric products. Since the amount of the rearranged product seemed to correlate with extended reaction times, the

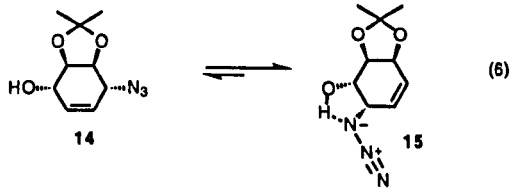


employment of a substrate that bore a better leaving group such as the dicarbonate **9b** was explored as a means to reduce the reaction time. Indeed, a 6:1 ratio of **10b**[4] and **11b**[4] was produced in 68% yield after only 7 h at r.t. using **2** as catalyst precursor. Surprisingly, using **12** as the palladium source gave a 3:1 ratio of **10b** to **11b** after only 3 h (57% yield). Significantly, lowering the amount of the palladium catalyst and using chiral ligand **13** in CH_2Cl_2 dramatically increased the amount of the 1,4-type product. For example, decreasing the amount of



catalyst from 2.5 mol% to 0.5 mol% as in eq 5 at 0° increased the ratio of ent-**10b**[4]:ent-**11b**[4] to >20:1 (84% yield). These results combined with the observation that no significant isomerization occurs thermally at these temperatures over several days suggest that the isomerization may also be palladium catalyzed.

A thermal isomerization does indeed occur. Heating ent-**10b** at 60° in THF leads to an equilibrium mixture of ent-**10b** and ent-**11b** of 1:3 from which the latter can be isolated in 63% yield. Further favoring of the rearranged 1,2-isomer under thermodynamic conditions was envisioned by converting the carbonate to the alcohol **15** since intramolecular hydrogen bonding is possible in this case but not for the regioisomer **14**.



Subjecting ent-**10b** to basic hydrolysis at 50° (K_2CO_3, CH_3OH) gave an approximate 1:9 ratio of **14**:**15** in full accord with this prediction. In this way, azide **15** was isolated in 82% yield. Thus, both the 1,4 and 1,2 substitution products are available.

In agreement with the mnemonic established for this asymmetric alkylation,[3] the clockwise type ligand **5** produced the mirror image products from those obtained from the counterclockwise type ligand **13**. The enantiopurity of ent-**10b** was established by way of the O-methylmandelic ester to be >95% ee.[10] Since ent-**11b** and **15** derived from ent-**10b**, by default, their ee's must also be >95%. As shown in the Table, the observed rotations for the enantiomeric products obtained from the two types of ligands were virtually equal in magnitude but opposite in sign, again supporting their high enantiopurity. Thus, both the diphenyl and cyclohexyl ligands gave excellent levels of asymmetric induction.

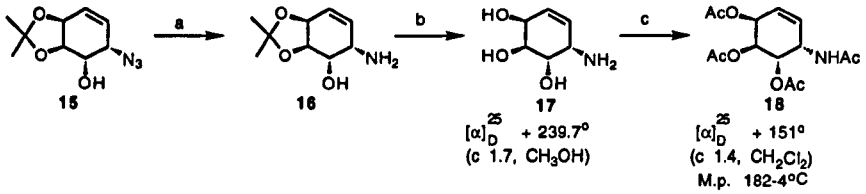
Table. Optical Rotations of Azidocarbonates

Ligand	1,4-Product	1,2-Product
5	+34.7° (c 1.4, CH_2Cl_2)[a]	-279° (c 2.0, CH_2Cl_2)[b]
13	-34.0° (c 1.4, CH_2Cl_2)[c]	+276° (c 2.1, CH_2Cl_2)[d]

a) **10b**, b) **11b**, c) ent-**10b**, d) ent-**11b**.

The availability of either regioisomer can prove quite valuable. For example, ent-**10b** has been converted into (+)-pancratistatin and N-benzoylconduramine A-1.[10] A synthesis of conduramine E (**17**) has now been completed from **15** as shown in Scheme 2. Simple Standinger type reduction to amine **16** followed by acid

Scheme 2. A Synthesis of (+)-Conduramine E



a) $(CH_3)_3P$, THF, H_2O, 94%. b) 2N HCl, H_2O, THF, 88%. c) Ac_2O, C_5H_5N, 70%

hydrolysis generated enantiopure conduramine E (**17**)[4] in 57% overall yield from dicarbonate **9b** and 40% overall yield from benzoquinone. It was further chracterized as its peracetate **18**.[4]

The combination of asymmetric synthesis of allylic azides and their subsequent [3.3] rearrangements provides two quite different substitution patterns in very simple fashion. The availability of such substitution diversity should prove valuable for the synthesis of complex aminoalcohols.

ACKNOWLEDGMENT: We thank the National Institutes of Health, General Medical Sciences and the National Science Foundation, for their generous support of our programs. Fellowship support for part of the stay of SRP from the American Cancer Society is gratefully acknowledged. Mass spectra were provided by the Mass Spectrometry Facility, University of California-San Francisco, supported by the NIH Division of Research Resources. We are indebted to Johnson Matthey Alfa Aesar for their generous loan of palladium salts.

REFERENCES

1. Gagneaux, A.; Winstein, S.; Young, W.G. *J. Am. Chem. Soc.* **1960**, *82*, 5956. Also see: Vanderwerf, C.A.; Heasley, V.L. *J. Org. Chem.* **1966**, *31*, 3534; Arimoto, M.; Yamaguchi, H.; Fujita, E.; Ochai, M.; Nagoa, Y. *Tetrahedron Lett.* **1987**, *28*, 6289; Chida, N.; Tobe, T.; Murai, K.; Yamazaki, K.; Ogawa, S. *Heterocycles* **1994**, *38*, 2383.
2. Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292. Also see: Tenaglia, A.; Waegell, B. *Tetrahedron Lett.* **1988**, *29*, 4851.
3. Trost, B.M.; Van Vranken, D.L.; Bingel, C. *J. Am. Chem. Soc.* **1982**, *114*, 9327.
4. This compound has been fully characterized spectrally and elemental composition established by combustion analysis and/or high resolution mass spectrometry.
5. Gololobov, Y.G.; Zhmurova, I.N.; Kasukhin, L.F. *Tetrahedron* **1981**, *37*, 437.
6. Trost, B.M.; Bunt, R.C.; Pulley, S.R. *J. Org. Chem.* **1994**, *59*, 4202.
7. For a review, see: Hudlicky, T.; Cebulak, M. "Cyclitols and Their Derivatives: A Handbook of Physical, Spectral, and Synthetic Data," VCH: New York, 1993. For recent reports by this group, see: Hudlicky, T.; Rouden, J.; Luna, H.; Olivo, H.F.; Anderson, C.; Nugent, T.; Price, J.D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907.
8. Johnson, C.R.; Plé, P.A.; Su, L.; Heeg, M.J.; Adams, J.P. *Synlett*, **1992**, 388.
9. Cambie, R.C.; Renner, N.D.; Rutledge, P.S.; Woodgate, P.D. *Syn. Commun.* **1989**, *19*, 537. Also see: Dumortier, L.; Liu P.; Dobbelaere, S.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 243.
10. Trost, B.M.; Pulley, S.R. *J. Am. Chem. Soc.* accepted for publication.

(*Received in USA* 8 *September* 1995; *revised* 28 *September* 1995; *accepted* 30 *September* 1995)