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Diversity-Oriented Synthesis of 2,4,6-Trisubstituted Piperidines via Type II Anion Relay Chemistry

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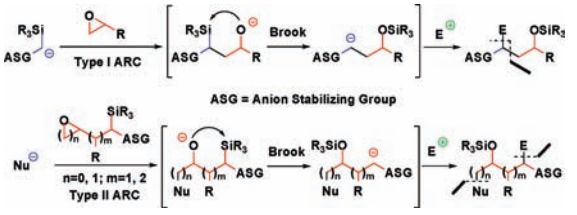
ABSTRACT

An effective, general protocol for the Diversity-Oriented Synthesis (DOS) of 2,4,6-trisubstituted piperidine congeners has been designed and validated. The successful strategy entails a modular approach to all possible stereoisomers of the selected piperidine scaffold, exploiting Type II Anion Relay Chemistry (ARC), followed in turn by intramolecular S_N2 cyclization, chemoselective removal of the dithiane moieties and carbonyl reductions.

Nature's biosynthesis of architecturally complex molecules often comprises iterative reaction sequences utilizing complex molecular machines, such as polyketide synthases and the ribosome, to unite activated, stereochemically pure building blocks.[1] In an attempt to mimic Nature's iterative biosynthesis of complex molecules, we developed and validated Type I and Type II Anion Relay Chemistry (ARC) (Scheme 1),[2] two closely related synthetic methods comprising multicomponent union protocols. In addition to providing access to specific architectures, the ARC tactic also holds considerable potential for Diversity-Oriented Synthesis (DOS).[3] Many DOS programs, however, suffer from the inability to provide access to all possible stereoisomers of a selected scaffold. We have therefore set as a goal for our DOS programs the construction of all stereoisomers of the selected scaffold. Such a goal, if widely adopted by the DOS community, will require, and in many cases demand, the development of new, innovative synthetic methods to access the targeted congeners in an efficient fashion, an outcome not dissimilar to one of the core goals of natural product total synthesis.

Scheme 1. Type I and Type II ARC



Having achieved the development and application of Type I Anion Relay chemistry (Scheme 1), initially as a tricomponent coupling protocol, which we employed to great advantage in a number of complex molecule synthetic programs,[4] we subsequently devised the Type II ARC tactic, also an iterative, multicomponent union strategy, which like the Type I ARC process exploits bifunctional

(1) Shen, B. *Curr. Opin. Chem. Biol.* **2003**, *7*, 285.

(2) (a) Smith, A. B., III; Wuest, W. M. *Chem. Commun.* **2008**, 5883. (b) Smith, A. B., III; Kim, W.-S.; Wuest, W. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7082. (c) Smith, A. B., III; Kim, W.-S.; Tong, R. *Org. Lett.* **2010**, *12*, 588. (d) Smith, A. B., III; Tong, R. *Org. Lett.* **2010**, *12*, 1260. (e) Smith, A. B., III; Kim, W.-S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6787.

(3) Schreiber, S. L. *Science* **2000**, *287*, 1964.

(4) (a) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191. (b) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196. (c) Smith, A. B., III; Pitram, S. M.; Fuertes, M. J. *Org. Lett.* **2003**, *5*, 2751. (d) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493. (e) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247. (f) Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547.

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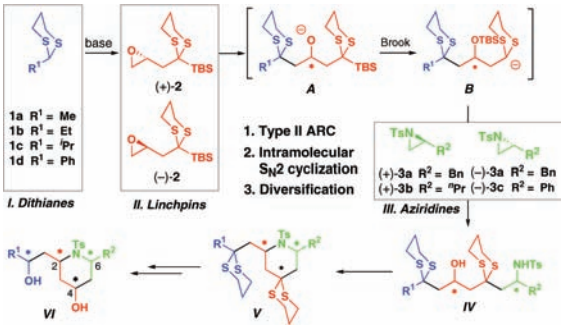
linchpins. The Type II ARC protocol holds, we believe, even more potential for the design and synthesis of complex molecular structures. The development of the Type II ARC process, however, required the design, synthesis, and validation of a series of effective bifunctional linchpins.[2]

To illustrate the utility of the Type II ARC tactic in the area of DOS, we report here the synthesis of all possible stereoisomers of a family of 2,4,6-trisubstituted piperidines (Scheme 2: ***VI***), utilizing this union tactic, followed in turn by an intramolecular S_N2 cyclization and further elaboration.

Scheme 2. General Synthetic Route To Access Diverse Piperidine Analogues via Type II ARC

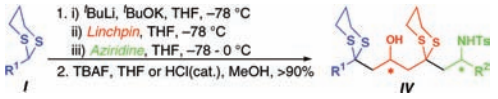


From the medicinal perspective, the piperidine scaffold has attracted considerable interest in the synthetic[5] and biological[6] communities. However, notwithstanding the availability of numerous methods to access individual members of the 2,4,6-trisubstituted piperidine family in a stereocontrolled fashion, there are few general methods that can provide access to all stereoisomers.[7]

The Type II ARC tactic, as illustrated in Scheme 2, not only would provide a convergent route to 2,4,6-trisubstituted piperidines, but also enables chemical and stereochemical diversification at the C(2) and C(6) stereogenic centers, depending on the components ***I***–***III*** employed. In addition, the two dithiane groups provide synthetic handles for further chemoselective diversification. To initiate this program, the three requisite components for the Type II ARC reaction were prepared: initiating nucleophiles ***I*** (dithianes **1a**–**d**), bifunctional linchpins ***II*** [(+)-**2**, (−)-**2**], and aziridines ***III*** [(+)-**3a**, (+)-**3b**, and (−)-**3a**, (−)-**3c**)], the latter readily accessible from enantiomerically pure amino acids.[8]

With these components in hand, reaction conditions for the Type II ARC protocol were optimized based on our earlier studies.[4] Conditions employing the modified Schlosser base[9] proved highly effective without the use of cosolvents such as HMPA or DMPU to enhance the nucleophilicity of dithiane anion.[10] The initial multicomponent adducts were subjected to removal of the TBS group with TBAF (Table 1).

Table 1. Multicomponent Reaction (Type II ARC)



entry	dithiane	linchpin	aziridine	config (*,*)[a]	yield[b] (%)
1	**1a**	(+)-**2**	(+)-**3a**	(*S*,*S*)-**4**	74
2	**1a**	(+)-**2**	(−)-**3a**	(*S*,*R*)-**4**	69
3	**1a**	(−)-**2**	(+)-**3a**	(*R*,*S*)-**4**	69
4	**1a**	(−)-**2**	(−)-**3a**	(*R*,*R*)-**4**	74
5	**1a**	(+)-**2**	(+)-**3b**	(*S*,*S*)-**5**	61
6	**1a**	(+)-**2**	(−)-**3c**	(*S*,*S*)-**6**	41
7	**1b**	(+)-**2**	(+)-**3a**	(*S*,*S*)-**7**	65
8	**1b**	(−)-**2**	(+)-**3a**	(*R*,*S*)-**7**	59
9	**1b**	(+)-**2**	(+)-**3b**	(*S*,*S*)-**8**	55
10	**1c**	(+)-**2**	(+)-**3a**	(*R*,*S*)-**9**	56
11	**1d**	(+)-**2**	(+)-**3a**	(*R*,*S*)-**10**	52
12	**1d**	(−)-**2**	(+)-**3a**	(*S*,*S*)-**10**	55

[a] Absolute configuration of the corresponding stereocenters. [b] Isolated yield for ARC.

Mesylation of the hydroxy group then furnished the substrates for the subsequent intramolecular S_N2 cyclizations. Examination of a variety of conditions, including solvents, bases, and leaving groups to suppress potential elimination reactions,[11] revealed that treatment of the mesylates in dilute THF solution with NaH effectively provided both 2,6-*cis*- and 2,6-*trans*-piperidines, again in preparatively useful yields (Table 2).

Next, the utility of the two dithiane groups was explored (Scheme 3). Treatment of (*R*,*S*)-**11** with $Hg(ClO_4)_2$ and 2,6-lutidine in wet THF led to regioselective removal of the more accessible side chain dithiane moiety to furnish ketone (*R*,*S*)-**14**, which in turn was subjected to various reduction conditions (Table 3A; entries 1–5). Use of the

(5) Recent examples, see: (a) Krishna, P. R.; Sreeshailam, A. *Tetrahedron Lett*. **2007**, *48*, 6924. (b) Chandraskhar, S.; Babu, G. S. K.; Reddy, Ch. R. *Tetrahedron: Asymmetry* **2009**, *20*, 2216. (c) Gnamm, C.; Krauter, C. M.; Brödner, K.; Helmchen, G. *Chem.—Eur. J*. **2009**, *15*, 2050. (d) Kumar, R. S. C.; Reddy, G. V.; Shankaraiah, G.; Babu, K. S.; Rao, J. M. *Tetrahedron Lett*. **2010**, *51*, 1114. (e) Cui, L.; Li, C.; Zhang, L. *Angew. Chem., Int. Ed*. **2010**, *49*, 9178.

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(7) Recent reviews:(a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (b) Weintraub, J. S.; Sabol, P. M.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (d) Cossy, J. *Chem. Rec*. **2005**, *5*, 70.

(8) Alonso, D. A.; Andersson, P. G. *J. Org. Chem*. **1998**, *63*, 9455.

(9) Schlosser, M.; Strunk, S. *Tetrahedron Lett*. **1984**, *25*, 741.

(10) Reich, H. J.; Sanders, A. W.; Fielder, A. T.; Bevan, M. J. *J. Am. Chem. Soc*. **2002**, *124*, 13386.

(11) Elimination reaction: see the Supporting Information for details.

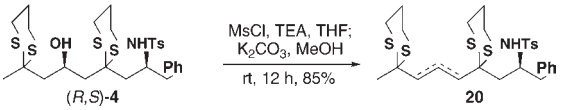
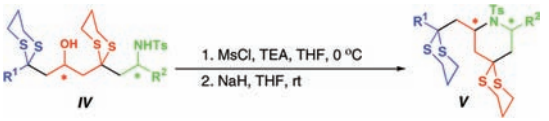


Table 2. Intramolecular S_N2 Cyclization

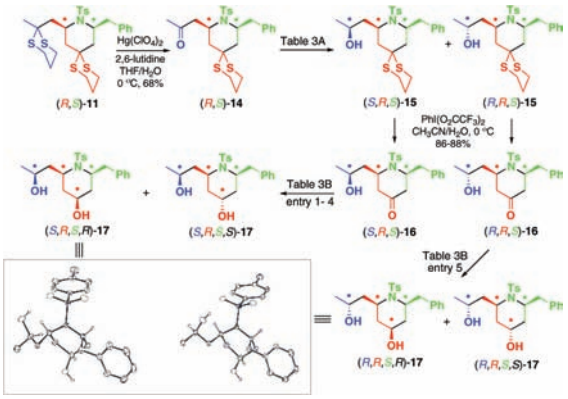


entry	substrate (*,*)[a]	R^1/R^2	product (*,*)[a]	ring substitution	yield[b] (%)
1	(*S*,*S*)-**4**	Me/Bn	(*R*,*S*)-**11**	*cis*	87
2	(*R*,*R*)-**4**	Me/Bn	(*S*,*R*)-**11**	*cis*	85
3	(*S*,*R*)-**4**	Me/Bn	(*R*,*R*)-**11**	*trans*	55
4	(*R*,*S*)-**4**	Me/Bn	(*S*,*S*)-**11**	*trans*	58
5	(*S*,*S*)-**5**	Me/^{n}Pr	(*R*,*S*)-**12**	*cis*	89
6	(*R*,*S*)-**10**	Ph/Bn	(*S*,*S*)-**13**	*cis*	81

[a] Absolute stereochemistry of the chiral center. [b] Yield over two steps.

Corey (*R*)-CBS reagent[12] (Table 3A; entry 4) and Al(O^{i}Pr)$_3$ (Table 3A; entry 5) proved optimal. The resultant diastereomeric alcohols (*S*,*R*,*S*)-**15** and (*R*,*R*,*S*)-**15**, readily separable by column chromatograpy, were then subjected to removal of the remaining dithiane moiety under the Stork conditions[13] to provide hydroxy ketones (*S*,*R*,*S*)-**16** and (*R*,*R*,*S*)-**16**.

Scheme 3. Functional and Stereochemical Diversification of 2,6-*Cis*-Disubstituted Piperidine (*R*,*S*)-**11**



Ketones **16** were also subjected to various reduction conditions. Regardless of steric encumberance of the hydride reducing agent, (*S*,*R*,*S*)-**16** led to β-hydroxy isomer (*S*,*R*,*S*,*R*)-**17** as the major diastereomer (Table 3B; entries 1−3). Molecular mechanics calculations (MMFF94) revealed that the 2,6-diaxial chairlike conformer ***C*** possesses a lower

Table 3. Screening Conditions for Reduction of Ketones

A. Reduction of (*R*,*S*)-**14**

entry	condition	product ratio[a] (*S*,*R*,*S*)-**14**:(*R*,*R*,*S*)-**14**	yield[b] (%)
1	A	2:1	93
2	B	3:1	97
3	C	4:1	92
4	D	1:20	93
5	E	5:1	88

B. Reduction of (*S*,*R*,*S*)-**16** (Entries 1−4) and (*R*,*R*,*S*)-**16** (Entry 5)

entry	condition	product ratio[a] (*S*,*R*,*S*,*R*)-**17**:(*S*,*R*,*S*,*S*)-**17**	yield[b] (%)
1	A	5:1	93
2	B	20:1	97
3	F	2:1	95
4	G	1:1.5	89
5	G	1:1.3[c]	91

[a] Ratio of diastereomers was determined by ^{1}H NMR. [b] Combined yield of diastereomers. [c] The ratio of (*R*,*R*,*S*,*R*)-**17**: (*R*,*R*,*S*,*S*)-**17**, conditions: (**A**) $NaBH_4$, MeOH, 0 °C; (**B**) L-Selectride, THF, −78−0 °C; (**C**) (*R*)-CBS reagent, $BH_3\cdot$THF, THF, 0 °C; (**D**) (*S*)-CBS reagent, $BH_3\cdot$THF, THF, 0 °C; (**E**) Al(O^{i}Pr)$_3$, ^{i}PrOH, reflux; (**F**) $BH_3\cdot$THF, THF, −78−0 °C; (**G**) SmI_2, H_2O, THF, −78−0 °C.

energy, by ca. 16 kcal/mol than the 2,6-diequatorial chairlike conformer ***D***, due to pseudo A^{1,3}-strain[14] between the substituents at the 2- and 6-positions and the tosyl group, thus leading to hydride attack from the more accessible α-face of ***C*** (Figure 1). In accordance with this reasoning, an increase in the bulkiness of the hydride reagent (L-Selectride) led to excellent selectivity (ca. 20:1) to provide (*S*,*R*,*S*,*R*)-**17** (Table 3B; entry 4).

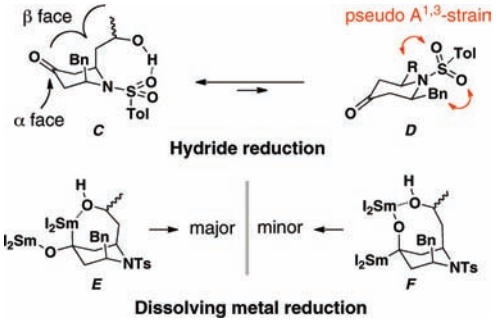


Figure 1. Proposed conformational analysis for the reduction of (*S*,*R*,*S*)-**16** and (*R*,*R*,*S*)-**16**.

At this juncture, we presumed that the diastereoselectivity could be reversed under dissolving metal conditions[15] to obtain diastereomer (*S*,*R*,*S*,*S*)-**17**. Treatment of (*S*,*R*,*S*)-**16** with SmI_2 (4.0 equiv) and H_2O (6.0 equiv) in THF furnished

(12) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861.

(13) (a) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem.* **2001**, *66*, 6502. (b) Stork, G.; Zhao, K. *Tetrahedron* **1989**, *30*, 287.

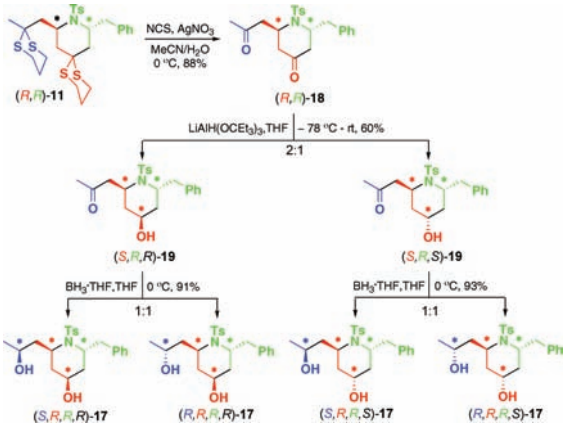
(14) (a) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010. (b) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. (c) Heintzelman, G. R.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 4594. (d) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867. (e) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747. (f) Cariou, C. A. M.; Snaith, J. S. *Org. Biomol. Chem.* **2006**, *4*, 51–53.

(15) (a) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187. (b) Keck, G. E.; Wager, C. A.; Seel, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172. (d) Keck, G. E.; Wager, C. A. *Org. Lett.* **2000**, *2*, 2307.

the desired α-hydroxy isomer as the major product, albeit with poor selectivity (Table 3B; entry 4). The lack of diastereoselectivity in the dissolving metal reductions presumably arises from competition of the two possible chelated intermediates (Figure 1; ***E*** and ***F***). The structures and the relative configurations of (*S,R,S,R*)-**17** and (*R,R,S,R*)-**17** were confirmed by X-ray crystallographic analysis. Under the same reduction conditions, (*R,R,S,R*)-**17** and (*R,R,S,S*)-**17** were obtained from (*R,R,S*)-**16** (Table 3B; entry 5).

On the basis of the successful elaboration of the 2,6-*cis*-piperidine congeners from (*R,S*)-**11**, the 2,6-*trans* congener (*R,R*)-**11** was subjected to the same procedure.[16] Following selective removal of the less-hindered dithiane moiety of (*R,R*)-**11**, all attempts to arrive at a single diastereomeric alcohol employing a wide variety of reducing agents proved unsuccessful. Equally disappointing, separations of the two diastereomeric alcohols (*S,R,R*)-**15**/(*R,R,R*)-**15** as well as the hydroxy ketones (*S,R,S*)-**16**/(*R,R,S*)-**16** could not be achieved.

Scheme 4. Functional and Stereochemical Diversification of 2,6-*Trans*-Disubstituted Piperidine (*R,R*)-**11**



To solve this issue, we explored the regioselective reduction of dione (*R,R*)-**18** (Scheme 4), which was generated by removal of the both dithiane moieties in (*R,R*)-**11** employing the Corey–Erickson protocol.[17] Pleasingly, the internal ketone of (*R,R*)-**18** was reduced regioselectively upon treatment with 1.0 equiv of the bulky reducing agent [$LiAlH(OCEt_3)_3$] to provide a mixture of (*S,R,R*)-**19** and (*S,R,S*)-**19**, readily separable by flash column chromatography. Reduction of the remaining side chain ketone employing $BH_3 \cdot THF$ furnished mixtures (ca. 1:1) of diastereomeric diols [(*S,R,R,R*)-**17**/(*R,R,R,R*)-**17** and (*S,R,R,S*)-**17**/(*R,R,R,S*)-**17**], which were separated by SFC, thereby providing access to all possible stereoisomers obtainable from (*R,R*)-**11**. Identical synthetic steps were followed with (*S,R*)-**11** and (*S,S*)-**11** to prepare the enantiomeric library *ent*-***A***.

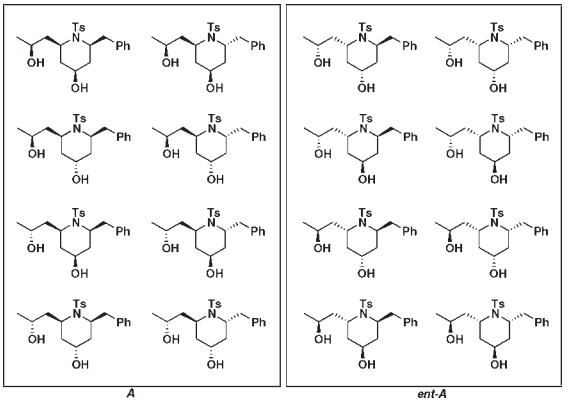


Figure 2. Complete piperidne library.

In summary, an effective DOS strategy has been designed and validated to access the complete matrix of stereoisomers of the targeted 2,4,6-trisubsituted piperidine scaffold, exploiting our modular Type II ARC protocol, followed in turn by intramolecular S_N2 cyclization (Figure 2). Regioselective dithiane removal and reduction conditions were then examined and optimized. In the context of complex molecule synthesis, the reported nonselective reductions would be viewed as a shortcoming. However for Diversity Oriented Synthesis (DOS) directed at the construction of a complete matrix of congeners, nonselective reactions in conjunction with effective chromatographic separation has considerable advantage. Nonetheless, the lack of observed selectivity serves to reveal a continuing need to develop new, selective reactivity to enhance the synthetic arsenal.

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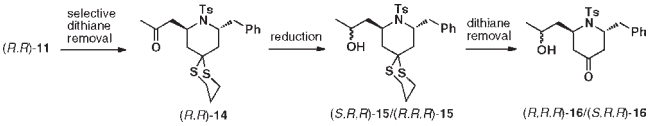
Supporting Information Available. Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) See the Supporting Information for details.



(17) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.