Organic LETTERS

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

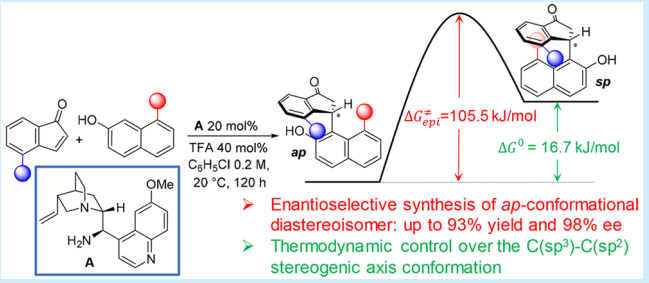
# Controlling the C(sp$^3$)−C(sp$^2$) Axial Conformation in the Enantioselective Friedel−Crafts-Type Alkylation of β-Naphthols with Inden-1-ones

Nicola Di Iorio, Giacomo Filippini, Andrea Mazzanti, Paolo Righi, and Giorgio Bencivenni*

Department of Industrial Chemistry "Toso Montanari", Alma Mater Studiorum-University of Bologna, Viale del Risorgimento 4, 40136 Bologna, Italy

Supporting Information

**ABSTRACT:** The Friedel−Crafts-type reaction between properly functionalized inden-1-ones and 2-naphthols generates a hindered single bond which displays a unique preference for an antiperiplanar conformational diastereoisomer. The steric hindrance and the presence of an enantioenriched stereogenic center control the distribution of the two diastereomeric conformers at equilibrium and increase the energy for the rotation of the C(sp$^3$)−C(sp$^2$) single bond.

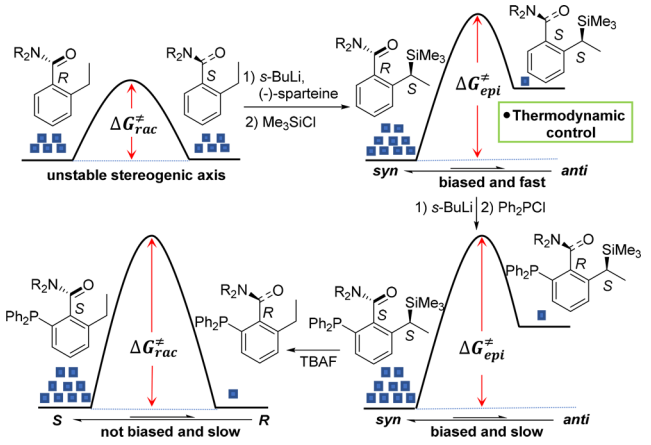



Atropisomers are compounds that have a stereogenic axis along a single bond with a hindered rotation. By tradition, the minimum energy barrier required to have a stable stereogenic axis is 96 kJ/mol at 300 K, thus ensuring a $t_{1/2}$ of racemization of 15 min.[1] The steric hindrance that surrounds the stereogenic axis is fundamental to provide the conformational stability. Atroposelective syntheses are realized with different methods such as dynamic kinetic resolution (DKR), desymmetrization, coupling, and arene-forming reactions.[2]

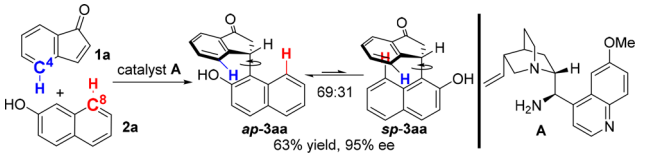
Enantioenriched atropisomers, in particular, nonbiaryl atropisomers, can also be obtained under thermodynamic control over two equilibrating conformational diastereoisomers (Scheme 1).[3] This strategy consists of a synthetic sequence wherein a compound with an unstable stereogenic axis is converted into a mixture of enantiomerically pure diastereomeric conformers by an enantioselective transformation. The new stereogenic center exerts the thermodynamic control on the conformation of the adjacent stereogenic axis by means of steric interactions. Finally, the installation of a large substituent increases the rotational energy of the stereogenic axis and fixes the configuration stability over time. The removal of the chiral inductor releases an enantioenriched mixture of atropisomers.[4]

During our previous study on the asymmetric Friedel−Crafts (F−C) alkylation of β-naphthol (**2a**) with inden-1-one (**1a**), we obtained the enantioenriched product **3aa** as a 69:31 equilibrium mixture of two diastereomeric conformers ***ap*-3aa** and ***sp*-3aa** due to a slow rotation around the new C(sp$^3$)−C(sp$^2$) bond (Scheme 2).[5]

**Scheme 1. Example of Thermodynamic Resolution**




**Scheme 2. Asymmetric Friedel−Crafts-Type Alkylation**




From NMR experiments, we assigned the antiperiplanar conformation to the major conformer ***ap*-3aa** with the C$^3$H directed toward the naphthol peri-hydrogen and the synperiplanar conformation to the minor conformer ***sp*-3aa** with the C$^3$H directed toward the OH group of naphthol. The energy barrier to rotation of the C(sp$^3$)−C(sp$^2$) stereogenic axis ($\Delta G^{\ddagger}_{epi}$) for the ***ap*-3aa** to ***sp*-3aa** interconversion was determined to be 74.5 kJ/mol by means of dynamic NMR

**Received:** November 1, 2017

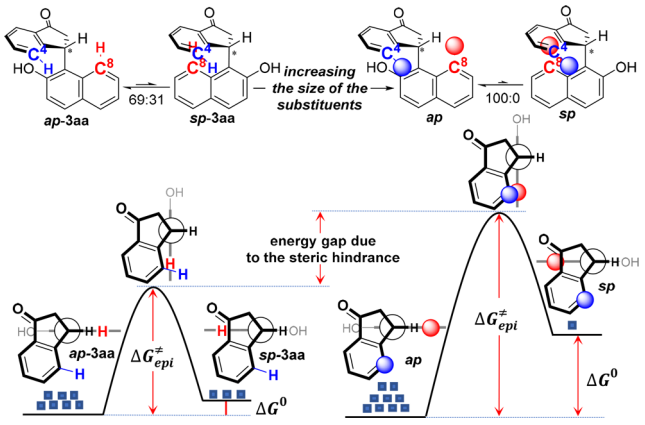




DOI: 10.1021/acs.orglett.7b03415
Org. Lett. XXXX, XXX, XXX−XXX

experiments. In light of this equilibrium, we speculated on the possibility of synthesizing a single enantiomerically enriched conformational diastereoisomer through thermodynamic control over a C(sp$^3$)−C(sp$^2$) stereogenic axis conformation. We rationalized that large substituents at C(8) of the naphthol and at C(4) of the indanone together with the presence of a stereogenic center directly bonded to the stereogenic axis could enhance the gap between the ground-state energies of the two conformers giving access to a single enantiomerically enriched diastereoisomeric conformer (Scheme 3).

**Scheme 3. Strategic Plan for the Construction of C(sp$^3$)−C(sp$^2$) Conformational Diastereoisomers**



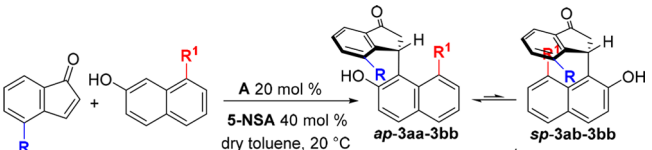

Furthermore, the larger steric hindrance should increase the barrier to rotation of the single bond, thus yielding atropisomers. This would be important because C(sp$^3$)−C(sp$^2$) atropisomers are well-known,[6] but their catalytic enantioselective synthesis has never been reported.

We set out to replace the hydrogen atoms with bulkier groups at either the β-naphthol or inden-1-one and then in both partners and measure the barrier for the ***ap***- to ***sp***-interconversion. The reactions were performed using a 20 mol % of 9-amino-9-deoxy-*epi*-quinidine **A** and 40 mol % of 5-nitrosalycylic acid (5-NSA) in dry toluene at 40 °C for 120 h. The results for compounds **3ab**, **3ba**, and **3bb** are displayed in Table 1 and compared with those for product **3aa**.

The reaction between inden-1-one **1a** and *N*-Boc-8-amino-β-naphthol **2b** gave compound **3ab** as a 90:10 mixture of conformational diastereoisomers ***ap*-3ab** and ***sp*-3ab** with a 63% ee. The rotational barrier was determined to be 83.7 kJ/mol by means of 1D-EXSY experiment in $C_2D_2Cl_4$ at 50 °C.[7] We then studied the reaction of 4-bromoindenone **1b** with β-naphthol **2a** at 20 °C. The desired product **3ba** was isolated in 62% yield and 78% ee. Also, in this case, an 86:14 mixture of ***ap*-3ba** and ***sp*-3ba** was observed at $^1$H NMR in DMSO-$d_6$. The rotational barrier was found to be 92.1 kJ/mol by 1D-EXSY experiment in DMSO-$d_6$ at 95 °C. The synergic effect of both substituents was then tested. The reaction of **1b** and **2b** furnished ***ap*-3bb** as a single conformational diastereoisomer in 40% yield and 60% ee. The minor conformer ***sp*-3bb** was not observed in the crude reaction mixture, and this prevented determination the value of $\Delta G^{\ddagger}_{epi}$.

Having established that the reaction could be realized with highly encumbered substrates, we then optimized the conditions. It was found that catalyst **A** (20 mol %) in combination with TFA (40 mol %) in chlorobenzene (0.2 M), furnished the best yield, enantioselectivity and diastereoselectivity.[8] Since we observed a partial degradation of the F−C products **3**, they were acetylated in situ immediately after the reaction to the corresponding compounds **4**. The scope of the F−C-type reaction was explored (Table 2). All of the reactions gave exclusively the ***ap***-conformer with elevated enantioselectivity. Different 8-substituted-β-naphthols **2b−j** were reacted in combination with 4-bromoindenone **1b**. The isolated yields ranged from moderate to very good and the enantioselectivity was very high except for compounds ***ap*-4bb** and ***ap*-4bc** with NHBoc and NHCbz substituents. The presence of electron-withdrawing (Br, Cl, I) and -releasing groups (OMe, *tert*-butyldimethylsilyloxy) was well tolerated and indanones ***ap*-4bd−bh** were obtained with high enantiocontrol. β-Naphthols with aromatic substituents gave the desired products ***ap*-4bi** and ***ap*-4bj** with good yields and excellent ee's.

**Table 1. Effect of the Steric Hindrance**[a]




**1a:** R = H
**1b:** R = Br
**2a:** R$^1$ = H
**2b:** R$^1$ = NHBoc
**3aa**: 63% yield,[b] 63% ee[c]
**3ab**: 40% yield,[b] 95% ee[c]
**3ba**: 62% yield,[b] 78% ee[c]
**3bb**: 40% yield,[b] 60% ee[c]

| entry | R | R$^1$ | *ap*/*sp*[d] | $\Delta G^{\ddagger}_{epi(exp)}$[e] | $\Delta G^{\ddagger}_{epi\ (calc)}$[e,f] |
|---|---|---|---|---|---|
| 3aa | H | H | 69:31 | 74.5 | |
| 3ab | H | NHBoc | 90:10 | 83.7[g] | 72.7 |
| 3ba | Br | H | 86:14 | 92.1 | 79.0 |
| 3bb | Br | NHBoc | 100:0 | n.d. | 105.5 |

[a]Reactions performed using 0.2 mmol of **1** and 0.22 mmol of **2** in 1 mL of toluene. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Determined by $^1$H NMR of the crude mixture. [e]In kJ/mol. [f]Calculated via DFT at the B3LYP/6-31G(d) level. [g]Determined on the corresponding acetylated **4ab** via 1D-EXY experiment.

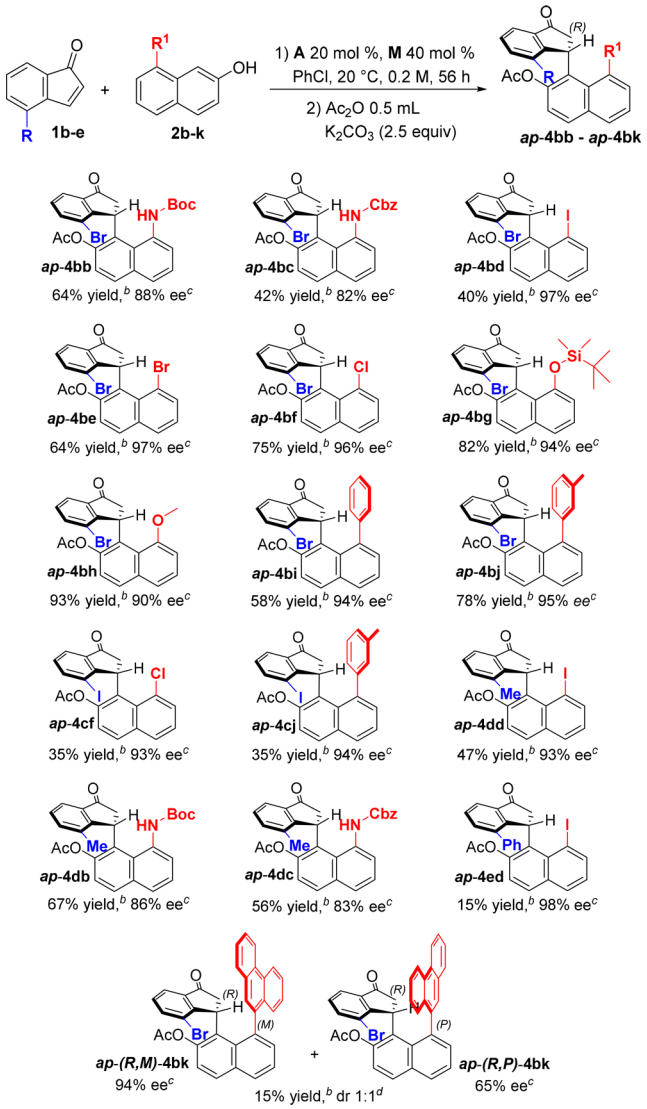
The reactivity of new inden-1-ones **1c−e** was investigated. Remarkably, electron-deficient **1c** and electron-rich derivatives **1d** and **1e** could be reacted with a variety of β-naphthols, giving successful results on the corresponding indanones ***ap*-4cf−dc**. Only **1e** was scarcely reactive. However, the desired product ***ap*-4ed** was obtained with a high ee. Interestingly, in the case of ***ap*-4bj** and ***ap*-4cj** a 56:44 mixture of conformers revealed the presence of a slow rotation of the C(sp$^2$)−C(sp$^2$) bond connecting naphthol with an *m*-tolyl substituent. We prepared β-naphthol **2k** bearing a phenanthryl substituent. The reaction with **1b** gave the desired compound in 15% yield as a 1:1 mixture of ***ap*-(*R*,*M*)-4bk** and ***ap*-(*R*,*P*)-4bk** diastereoisomers in a 94% and 65% ee, respectively. ***ap*-(*R*,*M*)-4bk** was isolated by preparative HPLC, and a $\Delta G^{\ddagger}_{epi}$ of 125.2 kJ/mol was measured for the rotation of the aryl−aryl bond. The *R* absolute configuration was assigned to compounds ***ap*-4bc** and ***ap*-4bf** and the *S* to compound ***ent*-*ap*-4bd** by means of single-crystal X-ray diffraction analyses.

The experimental trends are consistent with our hypothesis that large substituents and the concomitant presence of a stereogenic center, cooperate to control the formation of the thermodynamic ***ap***-conformational diastereoisomer and to increase the $\Delta G^{\ddagger}_{epi}$ measured for the ***ap***- to ***sp***- interconversion. However, in the case of compounds with two substituents it is only possible to observe the thermodynamic effect on the conformer populations and not the kinetic effect on the rotational barrier because the minor conformer has never been



DOI: 10.1021/acs.orglett.7b03415
*Org. Lett.* XXXX, XXX, XXX−XXX

**Table 2. Scope of the F−C-Type Alkylation**[a]

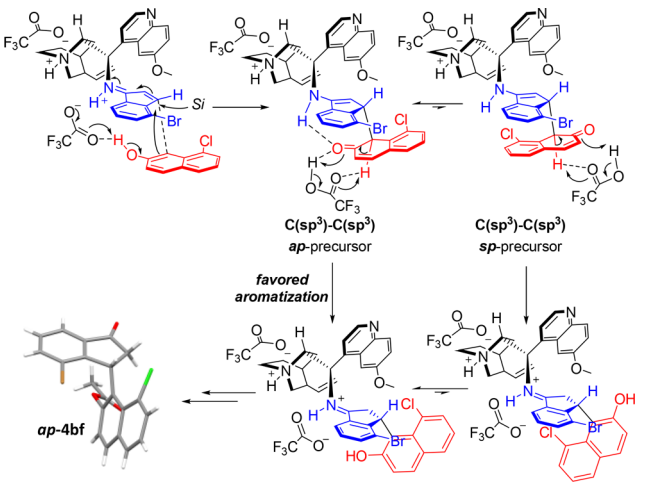



[a]Reactions performed with **1b−e** (0.2 mmol) and **2b−k** (0.22 mmol) in 1 mL of chlorobenzene. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Determined by $^1$H NMR.

detected. DFT calculation[9] suggested that ***sp*-3bb** is 16.7 kJ/mol higher in energy than ***ap*-3bb** and estimate an energy barrier for the ***ap*-3bb** to ***sp*-3bb** interconversion of 105.5 kJ/mol.[10] The huge 16.7 kJ/mol difference between the two ground states can easily explain why the ***sp*-conformation** (if produced by the reaction) cannot be detected after the reaction. The energy barrier for interconversion into the major conformer is 88.8 kJ/mol, a value that implies complete interconversion during the course of the 56 h of the reaction. This aspect does not exclude that our diastereomeric conformers are atropisomers.

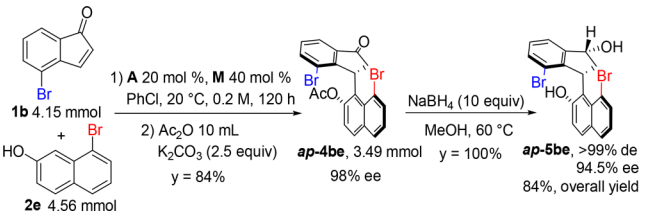
From the X-ray structures of ***ap*-4bf**, we can advance a transition state where the addition of **2f** takes place at the *Si* face of **1b**. A plausible model which minimizes the steric interactions and favors the approach at the *Si* face over the *Re* face of the iminium ion, can be rationalized using hydrogen bonding interactions between the catalytic salt and the hydroxy group of naphthol.[11] After the alkylation, only one of the two C(sp$^3$)−C(sp$^3$) intermediates in equilibrium with each other rapidly aromatizes to the most stable C(sp$^3$)−C(sp$^2$) conformational diastereoisomer (Scheme 4).

**Scheme 4. Proposed Catalytic Cycle**




As a final part of our work, we explored possible derivatizations of our products. We realized a large-scale catalytic reaction between **1b** and **2e** followed by reduction/deprotection of ***ap*-4be** with $NaBH_4$ in methanol at 60 °C. The desired indanol ***ap*-5be** was obtained in 84% overall yield and >99% de and 94.5% ee (Scheme 5).

**Scheme 5. Derivatization of Indanones**




In conclusion, by developing the reported enantioselective F−C-type alkylation between substituted indenones and naphthols we were able to exert thermodynamic control over the C(sp$^3$)−C(sp$^2$) stereogenic axis conformation and realize the selective synthesis of the ***ap*-conformational diastereoisomer**. The trend observed during the optimization would suggest the possible existence of this kind of compounds as novel C(sp$^3$)−C(sp$^2$) atropisomers. Further experiments are ongoing to study the feasibility of an atroposelective process.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03415.

General experimental procedures and characterization data for new compounds (PDF)

### Accession Codes

CCDC 1534642, 1534643, and 1534644 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.



DOI: 10.1021/acs.orglett.7b03415
Org. Lett. XXXX, XXX, XXX−XXX

uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## AUTHOR INFORMATION


### Corresponding Author

*E-mail: giorgio.bencivenni2@unibo.it.

### ORCID

Nicola Di Iorio: 0000-0002-4431-4007
Giacomo Filippini: 0000-0002-9694-3163
Andrea Mazzanti: 0000-0003-1819-8863
Paolo Righi: 0000-0003-1419-2560
Giorgio Bencivenni: 0000-0002-0855-1232


### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We are grateful to the University of Bologna for the financial support. We express our gratitude to Dr. Silvia Ranieri from the University of Bologna for her contribution for DFT calculations.

## REFERENCES


(1) (a) Ōki, M., Recent Advances in Atropisomerism. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Allinger, N. L., Eds.; John Wiley and Sons: New York, 2007; Vol. *14*, pp 1−81. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 1119−1181. (c) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561.

(2) (a) Shirakawa, S.; Liu, S.; Kaneko, S. *Chem. - Asian J.* **2016**, *11*, 330. (b) Bencivenni, G. *Synlett* **2015**, *26*, 1915. (c) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. *Chem. Rev.* **2015**, *115*, 11239. (d) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44*, 3418. (e) Baudoin, O. *Eur. J. Org. Chem.* **2005**, *2005*, 4223. (f) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (g) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (h) Witzig, R. M.; Lotter, D.; Fäseke, V. C.; Sparr, C. *Chem. - Eur. J.* **2017**, *23*, 12960.

(3) (a) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715. (b) Lee, W. K.; Park, Y. S.; Beak, P. *Acc. Chem. Res.* **2009**, *42*, 224. (c) Clayden, J. *Chem. Commun.* **2004**, 127. (d) Wolf, C. *Dynamic Stereochemistry of Chiral Compounds*; RSC Publishing: Cambridge, UK, 2008; pp 331−382.

(4) (a) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033. (b) Clayden, J.; Lai, L. W. *Tetrahedron Lett.* **2001**, *42*, 3163.

(5) (a) Paradisi, E.; Righi, P.; Mazzanti, A.; Ranieri, S.; Bencivenni, G. *Chem. Commun.* **2012**, *48*, 11178. For examples of restricted rotation of the $C(sp^3)-C(sp^2)$ single bond, see: (b) Delaye, P. O.; Lameiras, P.; Kervarec, N.; Mirand, C.; Berber, H. *J. Org. Chem.* **2010**, *75*, 2501. (c) Berber, H.; Lameiras, P.; Denhez, C.; Antheaume, C.; Clayden, J. *J. Org. Chem.* **2014**, *79*, 6015.

(6) (a) Nakamura, M.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2977. (b) Mori, T.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1199. (c) Lomas, J. S.; Dubois, J.-E. *J. Org. Chem.* **1976**, *41*, 3033. (d) Lomas, J. S.; Luong, P. K.; Dubois, J.-E. *J. Org. Chem.* **1977**, *42*, 3394. (e) Lomas, J. S.; Anderson, J. E. *J. Org. Chem.* **1995**, *60*, 3246. (f) Wolf, C.; Pranatharthiharan, L.; Ramagosa, R. B. *Tetrahedron Lett.* **2002**, *43*, 8563. (g) Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1997**, *62*, 3315. (h) Casarini, D.; Mancinelli, M.; Mazzanti, A.; Boschi, F. *Chirality* **2011**, *23*, 768. (i) Ford, T. W.; Thompson, T. B.; Snoble, K. A. J.; Timko, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 95. (j) Lomas, J. S.; Bru-Capdeville, V. *J. Chem. Soc., Perkin Trans. 2* **1994**, 459.

(7) Determined on the corresponding acetylated **4ab** via 1D-EXSY experiment. The ap/sp ratio after acetylation is 96:4.

(8) See the Supporting Informations for details.

(9) *Gaussian 09*, Revision D.01. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc.: Wallingford, CT, 2009.

(10) In the case of compound **4be**, DFT calculations estimated that the ***ap***-conformer is more stable than the ***sp***- by 16.3 kJ/mol. In the case of **3be**, the deacetylated form of **4be**, the same DFT calculation estimated a rotational energy barrier for the ***ap***- to ***sp*** interconversion of 107.5 kJ/mol. See the Supporting Information for details.

(11) Moran, A.; Hamilton, A.; Bo, C.; Melchiorre, P. *J. Am. Chem. Soc.* **2013**, *135*, 9091.




DOI: 10.1021/acs.orglett.7b03415
*Org. Lett.* XXXX, XXX, XXX−XXX