Synthesis of Vicinal Quaternary All-Carbon Centers via Acid-catalyzed Cycloisomerization of Neopentylic Epoxides

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ABSTRACT: We report our studies on the development of a catalytic cycloisomerization of 2,2-disubstituted neopentylic epoxides to produce highly substituted tetralins and chromanes. Termination of the sequence occurs via Friedel–Crafts-type alkylation of the remote (hetero)arene linker. The transformation is efficiently promoted by sulfuric acid and proceeds best in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent. Variation of the substitution pattern provided detailed insights into the migration tendencies and revealed a competing disproportionation pathway of dihydronaphthalenes.

Vicinal quaternary carbon centers are present in many bioactive natural products (e.g., salimabromide (1), lingzhiol (2), calycanthine (3), communesin F (4), and koumine (5)) and pharmaceuticals such as buprenorphine (6) (Scheme 1A). The presence of these structural units was reported to increase the structural rigidity allowing for tighter binding to their molecular targets in many cases and greater selectivity than with more flexible congeners.7 In nature, all-carbon quaternary centers are, for instance, accessible via reactions that proceed via carbocation intermediates.8,9 For their construction in the chemical laboratory, a well-assorted toolbox has been established in the past.5,6 However, synthetic challenges remain, as multistep procedures that are accompanied by low-yielding transformations are often required.

In the context of the synthesis of salimabromide (1), we were investigating methods to efficiently construct the fully substituted tetralinophenanthrene core.10 We found that ring formation and installation of the two crucial vicinal quaternary carbon centers were possible in a single step by means of a powerful cycloisomerization reaction of a 2,2-disubstituted neopentylic epoxide. This chemistry was inspired by the seminal reports by Bogert12 and Cook13 in 1933 (Scheme 1B). In this work, a tandem hydride migration/Friedel–Crafts-type cyclization of tertiary alcohol 7 enabled the synthesis of octahydrophenanthrene system 8. In 2010, Khalaf extended the rearrangement–cyclization cascade by resorting to acyclic tertiary alcohols such as 9 to enable installation of two vicinal gem-dimethyl groups.14

Unfortunately, both of these reports were strictly limited to a few unfunctionalized hydrocarbon frameworks. Herein we disclose the synthesis of vicinal all-carbon quaternary centers by the consecutive 1,2-rearrangement/cyclization of 2,2-disubstituted neopentylic epoxides under mild conditions (Scheme 1C). Selective migration of various alkyl residues was achieved by exploiting ring strain, carbon–carbon bond strengths, and carbocation stabilities. This allowed for the synthesis of a library of polyfunctionalized tetralin and chromane systems.

For the initial optimization of the reaction conditions, we employed readily available electron-rich arene 11a (Scheme 2A). We were pleased to find that the cycloisomerization proceeded most efficiently in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)5 at 0 °C with sulfuric acid (10 mol %) as catalyst, affording tetralin 12a in 83% yield within 15 min. Alternative solvents and Brønsted or Lewis acids were found to be inferior and led to significantly reduced yields (entries 2–7).15 Higher temperatures (23 °C, entry 9; 58 °C, entry 8) were less effective for this transformation, leading to complex mixtures of uncyclized byproducts.

With the optimized conditions in hand, we investigated the scope of the cycloisomerization in more detail (Scheme 2B). As a first parameter, we studied different aromatic residues as the nucleophilic component for the Friedel–Crafts termination step. Activating methyl and tert-butyl substituents provided yields of up to 83% (12c and 12d). Methoxy-substituted tetralins were obtained in virtually identical yields as for unsubstituted tetralin 12b, with only a little influence of the substitution pattern (69% for 12e and 70% for 12f). It is noteworthy that 12e was previously synthesized by the same cascade under nonoptimized conditions in only 43% yield.11 Remarkably, a fully methylated pyrogallol-derived epoxide...
formed the corresponding tetralin 12h in only 57% yield, while benzodioxole derivative 12g was isolated in 82%. We believe that this results from the trajectory of the approaching arene, which leads to severe steric interaction between the outer methoxy groups and the tertiary carbocation unit. As expected, substrates with deactivating substituents delivered the corresponding tetralins in only low yields or completely shut down the reaction (see Scheme 2D, limitations). Fluorinated tetralins 12i and 12j were formed in 35 and 41% yield, respectively. Pinacol boronate 12k, which is a valuable building block for further derivatizations via Suzuki–Miyaura cross-coupling reactions, was formed in 29% yield. Electron-rich, nonbasic heterocycles also proved to be compatible with the reaction conditions. For a thiophene substrate, efficient alkylation took place to afford the annealed 6/5-system 12l in 77% yield. Furans 12m and 12n were formed in lower yields under the reaction conditions, probably because of competing hydrolysis or polymerization.

We were pleased to see that the methodology is not limited only to aromatic nucleophiles: oxane 12o was formed in 43% yield from the corresponding primary alcohol. Interestingly, even for this relatively small nucleophile no oxolane formation was observed. This underpinned our assumption that the formation of a less-strained six-membered ring must be one of the major driving forces for the pinned assumption that the formation of a less-strained six-membered ring must be one of the major driving forces for the formation of a less-strained six-membered ring.

In an effort to investigate the requirements for successful 1,2 migration, we further modified the tert-butyl group and replaced one of the three methyl groups with an allyl, prenyl, benzyl, or vinyl group. Epoxide 17a afforded allyl-migrated tetralin 18a in 38% yield as the major product. Preferential migration of the weaker allylic bond was also observed for the prenyl substrate 17b. For this particular case, we observed protonation of the remote double bond of 18b and subsequent spiroxane formation with the neopentyl alcohol (39% yield of 19).

Scheme 1. Occurrence of Vicinal All-Carbon Quaternary Centers in Bioactive Molecules and Concept of this Work

A Vicinal Benzylic Quaternary Carbon Centers

B Preliminary Work

This Work

C This Work

- R = Me, Alkyl, Allyl, Vinyl, Ph, Br, H
- tetrals and chromanes
- mild conditions (0 °C, 15 min)
- high functional group tolerance
affording 18c in 36% yield. The competing methyl migration was also observed for this substrate, leading to the formation of 20 as a mixture of diastereomers (1.6:1 d.r.) in 19% yield. Careful analysis of the product mixture revealed the unusual 6/6/6/6-product 21 (hexahydrobenzo[c]phenanthrene) as the major product (41%). Despite the stronger sp²−sp³ bond (∼Bu−vinyl = 97.8 kcal mol⁻¹ vs t-Bu−methyl = 87.5 kcal mol⁻¹)⁻¹, the migration of a vinyl group was also observed to afford tetralin 18d in 22% yield together with a complex product mixture. The eight-membered-ring product 22, originating from at least two alkyl migration steps, was isolated as the only byproduct in 7% yield.¹⁹

To investigate the requirements for successful migratory cycloisomerization, we varied the degree of substitution of the terminal alkyl carbon starting with a methyl group (23a, R¹ = R² = R³ = H). As expected, no cycloisomerization was observed for this epoxide, but disproportionated naphthalene 27a (47%) and tetralin 28a (49%) were obtained in nearly quantitative combined yield. The same results were observed for substrates carrying an ethyl (23b) or benzyl (23c) group. When an isopropyl group was present, naphthalene 27d (29%) and tetralin 28d (34%) still prevailed. However, a 1,2-hydride shift was also observed to afford cycloisomerized tetralin 24d in 28% yield. Diphenylmethyl derivative 23e afforded the corresponding products in similar yields. Surprisingly, in this case only phenyl migration with low diastereoselective control (23e, 36% yield, 1.9:1 d.r.) was observed. Epoxide 11a, which was used for the optimization, delivered disproportionated naphthalene 27f (8%) and tetralin 28f (9%) under the reaction conditions. For the methoxymethyl group in substrate 23g, we
exclusively observed direct alkylation leading to a mixture of dihydronaphthalene 26g and its disproportionation products, the corresponding naphthalene 27g and tetralin 28g. Fast disproportionation was observed not only for dihydronaphthalenes but also for cycloisomerized neopentylic thiol 30. The use of thiirane 29 directly gave a mixture of desulfurized tetralin 31 (41%) and the corresponding disulfide 32 (22%).

While the disproportionation of thiols to disulfides and hydrogen is a common reaction, the formation of a hydrocarbon and a disulfide is unprecedented to the best of our knowledge.

Finally, we also screened a panel of chiral Lewis and Brønsted acid catalysts employing substrates 11a and 17d. Unfortunately, we did not observe any asymmetric induction (see the Supporting Information for screening). It is noteworthy that for all of the substrates investigated, no five- or seven-membered-ring systems were observed.

In conclusion, we have reported a powerful cycloisomerization reaction of 2,2-disubstituted neopentylic epoxides. The reaction does not require transition metal catalysts and proceeds under mild conditions in HFIP as the solvent. Variation of the terminating nucleophile enabled rapid access to functionalized chromanes and tetralins featuring vicinal all-carbon quaternary centers. The use of cycloalkyl moieties allowed for the formation of tricyclic ring systems in one step. Analysis of the byproducts revealed fast disproportionation of dihydronaphthalenes to form naphthalenes and tetralins.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02296.
Experimental procedures, optimization screens, compound characterization, X-ray crystal structure data, computational studies, and spectral data (PDF)

Accession Codes
CCDC 2010932 contains 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.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

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REFERENCES

(1) Felder, S.; Dreisigacker, S.; Kehrzaus, S.; Neu, E.; Bierbaum, G.; Wright, P. R.; Menche, D.; Schäberle, T. F.; König, G. M. Salimabromide: Unexpected Chemistry from the Obligate Marine Myxobacteria Enhydromyxa salina. Chem. - Eur. J. 2013, 19, 9319.
(2) Yan, Y.-M.; Ai, J.; Zhou, L. L.; Chung, A. C. K.; Li, R.; Nie, J.; Fang, P.; Wang, X.-L.; Luo, J.; Hu, Q.; Hou, F.-F.; Cheng, Y.-X. Lingnols, Unprecedented Rotary Disk-Shaped Meroterpenoids as Potent and Selective Inhibitors of p-Smad3 from Ganoderma lucidum. Org. Lett. 2013, 15, 5488.
(3) Eccles, G. R. Total Synthesis of the Calycanthaceous Alkaloids. Proc. Am. Pharm. Assoc. 1888, 382.
(4) Hayashi, H.; Matsumoto, H.; Akiyama, K. New Insecticidal Compounds, Communesins C, D and E from Penicillium expansum Link MK-57. Biosci., Biotechnol., Biochem. 2004, 68, 753.
(5) Liu, C.-T.; Wang, Q.-W.; Wang, C.-H. Structure of Koumine. J. Am. Chem. Soc. 1981, 103, 4634.
(6) Heel, R. C.; Broden, R. N.; Speight, T. M.; Avery, G. S. Buprenorphine: A Review of its Pharmacological Properties and Therapeutic Efficacy. Drugs 1979, 17, 81.
(7) Juncosa, J. I.; Hansen, M.; Bonner, L. A.; Cueva, J. P.; Maglathlin, R.; McCorry, J. D.; Marona-Lewicka, D.; Lill, M. A.; Nichols, D. E. Extensive Rigid Analogue Design Maps the Binding Conformation of Potent N-Benzylphenethylamine 5-HT3 Serotonin Receptor Agonist Lands. ACS Chem. Neurosci. 2013, 4, 96.
(8) Peterson, E. A.; Overman, L. E. Contiguous Stereogenic Quaternary Carbons: A Daunting Challenge in Natural Products Synthesis. Proc. Natl. Acad. Sci. U. S. A. 2004, 101, 11943.
(9) Johnson, W. S. Biomimetic Polyene Cyclizations; Angew. Chem., Int. Ed. Engl. 1976, 15, 9.
(10) (a) Zheng, H.; Wang, Y.; Xu, C.; Xu, X.; Lin, L.; Liu, X.; Feng, X. Stereodivergent Synthesis of Vicinal Quaternary-Quaternary Stereocenters and Bioactive Hyperolactones. Nat. Commun. 2018, 9, 1968. (b) Long, R.; Huang, J.; Gong, J.; Yang, Z. Direct Construction of Vicinal All-Carbon Quaternary Stereocenters in Natural Product Synthesis. Nat. Prod. Rep. 2015, 32, 1584. (c) Quasdorf, K. W.; Overman, L. E. Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocenters. Nature 2014, 516, 181. (d) Büschele, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E. Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms. Angew. Chem., Int. Ed. 2016, 55, 4156.
(11) (a) Schmid, M.; Grossmann, A. S.; Mayer, P.; Müller, T.; Magauer, T. Ring-expansion Approaches for the Total Synthesis of Salimabromide. Tetrahedron 2019, 75, 3195. (b) Schmid, M.; Grossmann, A. S.; Wurst, K.; Magauer, T. Total Synthesis of Salimabromide: A Tetracyclic Polyketide from a Marine Myxobacterium. J. Am. Chem. Soc. 2018, 140, 8444.
(12) Bogert, M. T. A New Process for the Synthesis of Phenanthrene and of Phenanthrene Derivatives; Science 1933, 77, 289.
(13) Cook, J. W.; Hewett, C. L. The Synthesis of Compounds related to the Sterols, Bile Acids, and Oestrus-Producing Hormones. Part I. 1,2-Cyclopentenophenanthrene. J. Chem. Soc. 1933, 1098.
(14) Khalaf, A. A.; Albar, H. A.; El-Fouty, K. O. Modern Friedel-Crafts Chemistry. Part 301. Facile Synthesis of Isomeric Tri-and Tetramethyltetrahydrophenanthrenes via Rearranged Cycloalkylation of Suitably Methylated 1-(1- and 2-naphthyl)-3-pentanols. Indian J. Chem. 2010, 49B, 203.
(15) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a Highly Versatile Solvent. Nat. Rev. Chem. 2017, 1, 0088.
(16) For a full optimization table, see the Supporting Information. (17) In the case of 12n, the corresponding hydrolyzed diketone was isolated in 11% yield. (18) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of N-Benzylphenethylamine 5-HT3 Serotonin Receptor Agonist Lands. J. Med. Chem. 2001, 44, 3811. (19) For a proposed reaction mechanism, see the Supporting Information.
(20) The combined yield increased to 92% when trimethylsilyl trifluoromethanesulfonate was used instead of sulfuric acid.

(21) Choi, J.; Yoon, N. M. Synthesis of Disulfides by Copper-Catalyzed Disproportionation of Thiols. *J. Org. Chem.* 1995, *60*, 3266.

(22) The use of an enantiomerically enriched epoxide (82% ee) provided tetratin **12e** with 70% ee (see ref 11).

(23) This result was also supported by computational studies at the ωB97X-D/6-311G(d,p)/ SMD(F3CCCH2OH) level employing **11e** (see the Supporting Information for details).