α-Cyclodextrin Encapsulation of Bicyclo[1.1.1]pentane Derivatives: A Storable Feedstock for Preparation of [1.1.1]Propellane

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[1.1.1]Propellane is a highly strained molecule that represents the most convenient starting material for the synthesis of the bicyclo[1.1.1]pentane (BCP) unit, which is now widely recognized as a three-dimensional (3D) bioisostere of the benzene ring. Replacement of *para*-phenyl derivatives with 1,3-disubstituted BCP scaffolds can improve metabolic stability, solubility, and membrane permeability (Scheme 1A).[1] However, the lack of straightforward and versatile synthetic methodologies to access multi-functionalized BCP derivatives is a significant impediment to realizing the full potential of this promising scaffold.[2] To address this synthetic challenge and to contribute to the field of drug discovery, the group of Professor Masanobu Uchiyama from The University of Tokyo (Japan) started a project to develop innovative synthetic tools to access a variety of BCP derivatives.

"Synthetic methodologies that can access 3D drug-like scaffolds are very important in modern drug discovery," said Professor Uchiyama. "In particular, 3D scaffolds with higher F*sp*^{3} (fraction of sp^3 carbon atoms) values let us escape from the landscape of "flat" molecules and open up a much larger structural space, contributing to the development of drugs with superior physical properties and improved safety.[3]"

Professor Uchiyama explained that [1.1.1]propellane, which is now recognized as the key precursor of BCPs, features a remarkable inverted tetrahedral geometry at the bridgehead carbons. "The nature of the bond between the bridgehead carbons (covalent, charge-shift bond, singlet biradicaloid, or no bond) of [1.1.1]propellanes has been addressed in a number of theoretical and experimental studies, which have sometimes led to conflicting conclusions," said Professor Uchiyama: "In 2017, we reported a radical multicomponent carboamination of [1.1.1]propellane to form C–C and C–N bonds simultaneously on a BCP scaffold for the first time.[4] This reaction provides easy access to a wide range of novel multi-functionalized BCP derivatives. These products are easily transformed into a variety of synthetically useful drug-like 3-functionalized BCP-amines. Thus, this methodology opened up previously inaccessible drug-like chemical spaces."

"In subsequent work, we focused on the creation of a versatile synthetic platform for BCP scaffolds. Commonly used BCP intermediates have symmetrical structures, and multiple synthetic operations are needed to transform them into unsymmetrically functionalized BCP derivatives," said Professor Uchiyama. He continued: "In 2020, we developed a silaboration of [1.1.1]propellane, enabling direct introduction of B and Si functional groups onto the BCP scaffold.[5] The silylborated BCP can be obtained on a gram scale in a single step without the need for column-chromatographic purification, and is storable as well as easy to handle. Thus, it serves as a versatile synthetic intermediate, whose B–C and Si–C bonds can be used as footholds to access unsymmetrically 1,3-disubstituted BCP scaffolds."

The next challenge for the group was an efficient preparation of [1.1.1]propellane, which remains the most important precursor for BCP derivatives.[6] According to Professor Uchiyama, little progress has been made in the preparation of [1.1.1]propellane since the first practical synthesis in 1985 by Szeimies,[7] and several fundamental issues remain to be addressed (Scheme 1B). He then went on to list them: "(1) [1.1.1]propellane is currently synthesized from tetrahalide 1 and 2 equivalents of highly active organolithium reagent (MeLi or PhLi), and the reaction conditions must be strictly controlled; (2) [1.1.1]propellane thus synthesized is isolated by distillation and hence is obtained as an ethereal solution (normally in Et_2O), which can be problematic if the subsequent reaction requires a different solvent; (3) [1.1.1]propellane is thermally and chemically labile, so its solution should, in principle, be freshly prepared prior to use. In our paper, we describe α-cyclodextrin (α-CD) encapsulation of BCP derivatives, providing a bench-top-storable format for these derivatives," explained Professor Uchiyama. He continued: "We also developed simple protocols for deiodination reaction of 1,3-diiodo BCP (I–BCP–I) to afford [1.1.1]propellane. Together, these findings provide for the first time a simple methodology for on-demand preparation of [1.1.1]propellane in a wide range of solvents (protic/aprotic/polar/non-polar) under mild conditions (Scheme 1C)."

The group investigated host–guest complex formation with various host molecules (α-/β-/γ-CDs, calix[n]arenes (*n* = 4–6), pillar[*n*']arenes (*n*' = 5, 6), or 18-crown-6-ether), and serendipitously found that only α-CD gave a complex of I–BCP–I encapsulated in two molecules of α-CD. Surprisingly, the α-CD supramolecular capsule could incorporate a wide range of BCP derivatives: the corresponding ternary complexes of

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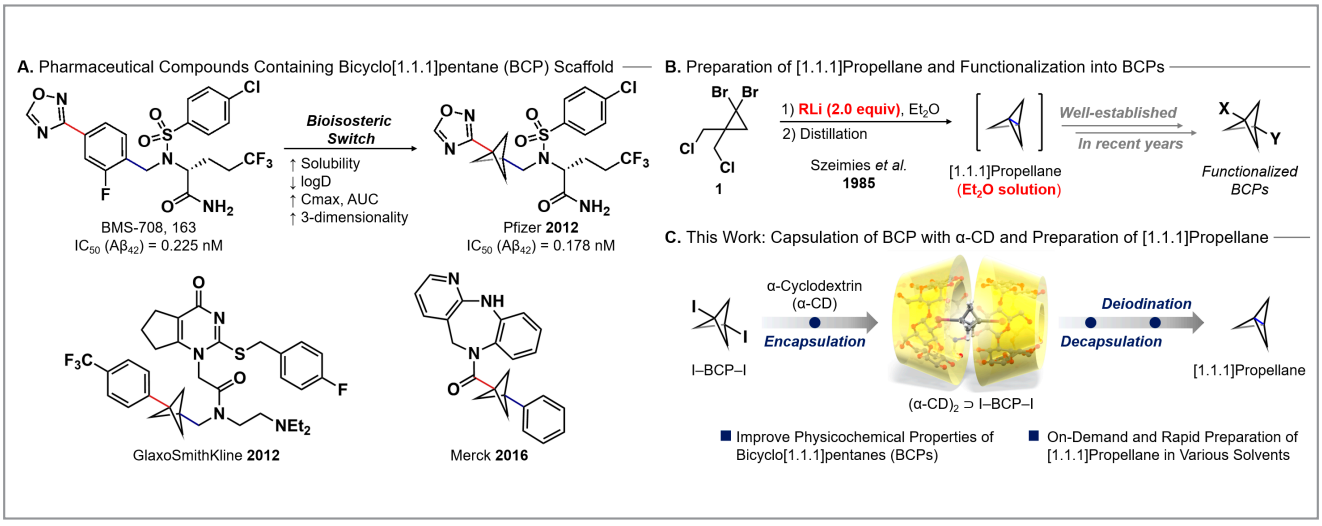
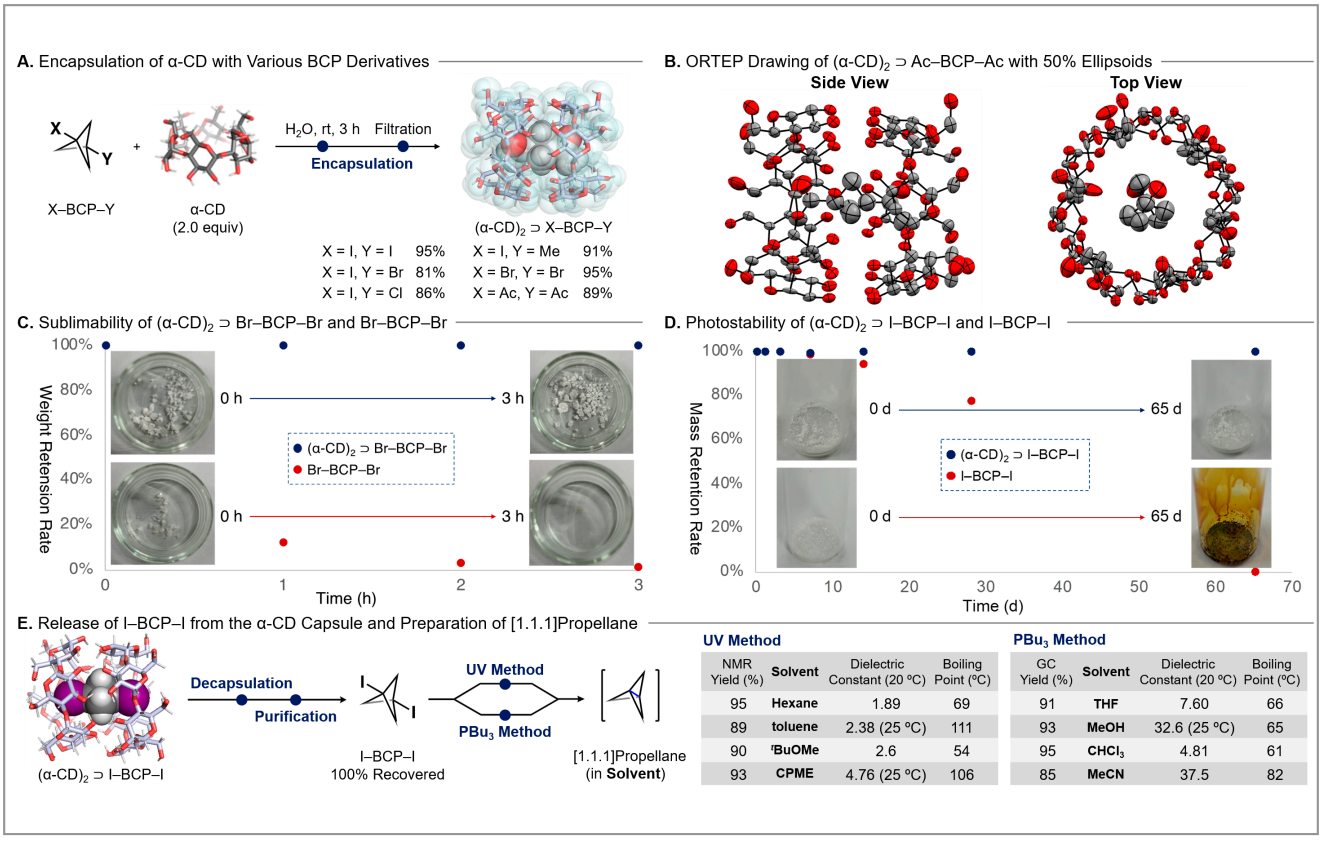


Scheme 1 (A) Pharmaceutical applications of the bicyclo[1.1.1]pentane (BCP) scaffold. (B) Preparation of [1.1.1]propellane by Szeimies *et al*. (C) This work.



UV Method

NMR Yield (%)	Solvent	Dielectric Constant (20 °C)	Boiling Point (°C)
95	Hexane	1.89	69
89	toluene	2.38 (25 °C)	111
90	^{t}BuOMe	2.6	54
93	CPME	4.76 (25 °C)	106

PBu_3 Method

GC Yield (%)	Solvent	Dielectric Constant (20 °C)	Boiling Point (°C)
91	THF	7.60	66
93	MeOH	32.6 (25 °C)	65
95	$CHCl_3$	4.81	61
85	MeCN	37.5	82

Scheme 2 (A) Encapsulation of α-CD and BCP derivatives. (B) X-ray crystal structure of $(\alpha\text{-CD})_2 \supset$ Ac–BCP–Ac (CCDC 2036538). (C) Sublimability of $(\alpha\text{-CD})_2 \supset$ Br–BCP–Br and Br–BCP–Br at 25 °C. (D) Photostability of $(\alpha\text{-CD})_2 \supset$ I–BCP–I and I–BCP–I under ambient air and fluorescent lighting conditions. (E) Release from α-CD capsule and optimized protocols for the preparation of [1.1.1]propellane.

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other 1,3-disubstituted BCPs (X–BCP–Y) were obtained in high yields (81–95%) (Scheme 2A). Professor Uchiyama remarked: "These complexes were precipitated in water and readily collected by simple filtration. A single-crystal X-ray diffraction analysis clearly showed the complete uptake of 1 equivalent of Ac–BCP–Ac inside the head-to-head dimeric α-CD capsule (Scheme 2B). Encapsulation affords great benefits to the synthetic chemistry of BCPs by overcoming the intrinsic disadvantages of BCP synthons, such as volatility, sublimability, and low boiling point. For example, encapsulation converted Br–BCP–Br, which is oily and volatile at room temperature, into a stable and easy-to-handle powder (Scheme 2C). In addition, the photostability of I–BCP–I was greatly improved by encapsulation (Scheme 2D). Thus, α-CD encapsulation endows BCPs with unprecedented chemical, thermal, photo-, and air-stability, and provides the first bench-top-storable source for these derivatives. Finally, we confirmed that the encapsulated I–BCP–I could be converted into [1.1.1]propellane, the gold-standard intermediate for BCP synthesis. As a result of various investigations, we developed a method for quantitative decapsulation and conversion of I–BCP–I to [1.1.1]propellane under mild conditions, enabling on-demand preparation of [1.1.1]propellane in a wide range of solvents (protic/aprotic/polar/nonpolar) (Scheme 2E).[8]"

Professor Uchiyama concluded: "We believe this methodology represents an important advance in the synthetic chemistry of BCPs and related 3D structures, and will expand the chemical space available for medicinal chemistry, synthetic chemistry, and materials sciences."

Biographical Sketches

From left: Prof. Dr. K. Miyamoto, Prof. Dr. M. Uchiyama, Prof. Dr. J. Kanazawa

Junichiro Kanazawa received his B.Sc. in 2011 and his M.Sc. in 2013 from The University of Tokyo (Japan) under the direction of Professor Masanobu Uchiyama. He has worked as a medicinal chemist at Japan Tobacco Inc. (Japan) from 2013, and has been a visiting researcher at RIKEN (Japan) since 2015. He received his Ph.D. in 2018 from the University of Tokyo under the direction of Professor Masanobu Uchiyama. He has been an Assistant Professor at the Graduate School of Pharmaceutical Sciences, The University of Tokyo since 2019. His research interests include the development of new reactions, and computational chemistry.

Kazunori Miyamoto received his Ph.D. in 2008 from the University of Tokushima (Japan). He was appointed as an Assistant Professor at the Graduate School of Pharmaceutical Sciences, University of Tokushima, in 2005. He moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo (Japan), as a Lecturer in 2014 and was promoted to Associate Professor in 2019. His research interests include hypervalent halogen compounds and the development of organic reactions based on the unique characteristics of the elements and compounds.

Masanobu Uchiyama received his Ph.D. in 1998 from The University of Tokyo (Japan). He was appointed as an Assistant Professor at the Department of Pharmaceutical Sciences, Tohoku University (Japan), in 1995. He moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo, as an Assistant Professor in 2001 and was promoted to Lecturer in 2003. He moved to RIKEN (Japan) as an Associate Chief Scientist (PI) in 2006. He has been a Professor at The University of Tokyo since 2010. He was promoted to Chief Scientist at RIKEN in 2013 (Joint Appointment), and is also a Professor of Research Initiative for Supra-Materials (RISM) at Shinshu University, Japan (Cross Appointment). His research interests include the development of new reactions, new materials, and new functions based on the integration of theoretical calculations and synthetic chemistry.

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