A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

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

Authors: Tadafumi Matsunaga, Junichiro Kanazawa, Tomohiro Ichikawa, Mei Harada, Yusuke Nishiyama, Nghia Tuan Duong, Takashi Matsumoto, Kazunori Miyamoto, and Masanobu Uchiyama

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202014997

Link to VoR: https://doi.org/10.1002/anie.202014997

WILEY-VCH

10.1002/anie.202014997

WILEY-VCH

COMMUNICATION

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

Tadafumi Matsunaga,[a] Junichiro Kanazawa,*[a] Tomohiro Ichikawa,[a] Mei Harada,[a] Yusuke Nishiyama,[b,c] Nghia Tuan Duong,[b] Takashi Matsumoto,[d] Kazunori Miyamoto,*[a] and Masanobu Uchiyama*[a,e,f]

[a] T. Matsunaga, Dr. J. Kanazawa, Dr. T. Ichikawa, M. Harada, Dr. K. Miyamoto, Prof. Dr. M. Uchiyama
Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
E-mail: j.kanazawa@mol.f.u-tokyo.ac.jp
E-mail: kmiya@mol.f.u-tokyo.ac.jp
E-mail: uchiyama@mol.f.u-tokyo.ac.jp
[b] Dr. Y. Nishiyama, N. T. Duong
RIKEN-JEOL Collaboration Center and SPring-8 Center, RIKEN, Tsurumi, Yokohama, Kanagawa 230-0045, Japan
[c] Dr. Y. Nishiyama
JEOL RESONANCE Inc., 3-1-2 Musashino, Akishima, Tokyo 196-8558, Japan
[d] Dr. T. Matsumoto
Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima, Tokyo, 196-8666, Japan
[e] Prof. Dr. M. Uchiyama
Cluster for Pioneering Research (CPR), RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan
[f] Prof. Dr. M. Uchiyama
Research Initiative for Supra-Materials (RISM), Shinshu University, 3-15-1 Tokida, Ueda, Nagano 386-8567, Japan

Supporting information for this article is given via a link at the end of the document.

Abstract: The bicyclo[1.1.1]pentane (BCP) scaffold is useful in medicinal chemistry, and many protocols are available for synthesizing BCP derivatives from [1.1.1]propellane. Here, we report (1) the α-cyclodextrin (α-CD) encapsulation of BCP derivatives, affording a stable, readily storable material from which BCPs can be easily and quantitatively recovered and (2) new and simple protocols for deiodination reaction of 1,3-diiodo BCP to afford [1.1.1]propellane in protic/aprotic/polar/non-polar solvents. The combination of these methodologies enables simple, on-demand preparation of [1.1.1]propellane in various solvents under mild conditions from α-CD capsules containing 1,3-diiodo BCP.

Bicyclo[1.1.1]pentane (BCP) has attracted increasing interest as a three-dimensional bioisostere for the phenyl ring to improve the pharmacokinetic profile of drug candidates, and typically increases metabolic stability, aqueous solubility, and membrane permeability.[1] Therefore, BCP is emerging as a standard candidate for spacer group replacement in drug evaluation (Figure 1A).[2] However, synthetic methods to install BCP into various skeletons are not yet well developed. Currently, the most promising approach to construct the BCP framework relies on the use of [1.1.1]propellane (**2**),[3] which features a remarkable "inverted" central σ-bond (Figure 1B). In recent years, a number of protocols to derivatize BCP have been developed based upon strain-release-driven reactions of [1.1.1]propellane.[4]

Thus, at present, the Achilles heel in the synthetic chemistry of BCP is the preparation of [1.1.1]propellane, and little progress has been made since the first practical synthesis by Szeimies and co-workers in 1985.[5] Unfortunately, their pioneering method has several limitations. For example, (1) the initial lithium-bromine exchange of tetrahalide (**1**) requires the use of 2 equiv. of MeLi, leading to the formation of 2 equiv. of MeBr (b.p. 4°C), which is difficult to separate from [1.1.1]propellane (b.p. ca. 30°C) by distillation. Baran and coworkers reported an improved method, in which PhLi is used instead, giving PhBr (b.p. 156°C) as the by-product.[4a] However, the use of these highly active organolithium reagents still requires great care. (2) [1.1.1]Propellane purified by distillation is obtained as an ethereal solution (typically in Et_2O),

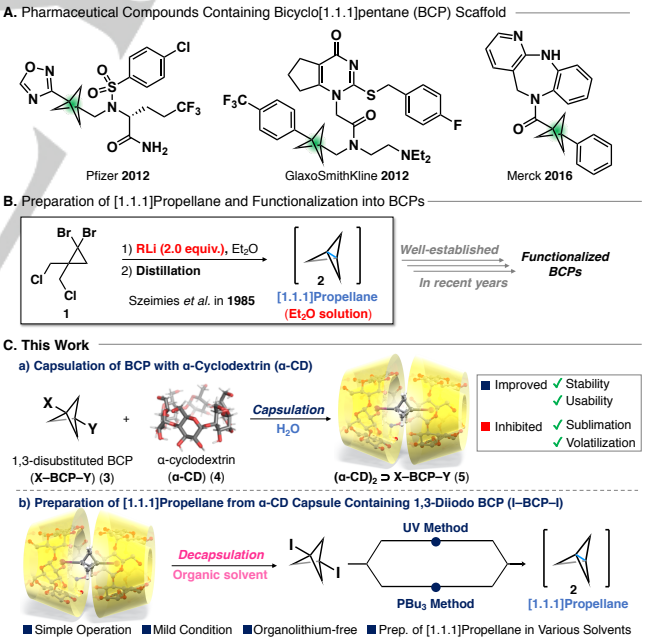


Figure 1. (A) Pharmaceutical applications of the bicyclo[1.1.1]pentane (BCP) scaffold. (B) Preparation of [1.1.1]propellane by Szeimies *et al.* (C) This work.

which can be problematic if the subsequent reaction requires a different solvent. In addition, (3) [1.1.1]propellane is thermally and chemically labile, and so it would be desirable to be prepared prior to use. To address these issues, our group recently developed a silaboration reaction of [1.1.1]propellane to give silaborated BCP (Si–BCP–B) in a single step on a gram scale as a stable precursor for unsymmetrically functionalized BCPs; however, available BCP–Si bond transformations were limited.[4m] Herein, we report the spontaneous host–guest complexation of 1,3-disubstituted BCP derivatives (X–BCP–Y) (**3**) with 2 equiv. of α-cyclodextrin (α-CD) (**4**) in water. The obtained complexes (**5**) serve as bench-top-storable BCP feedstocks with high chemical, thermal, and photo-stability (Figure 1C(a)). We further established new protocols to obtain [1.1.1]propellane from the encapsulated 1,3-diiodo BCP (I–BCP–I) complex (**5a**), thereby enabling the facile and flexible preparation of [1.1.1]propellane in a variety of solvents (protic/aprotic/polar/non-polar) under mild conditions (Figure 1C(b)).

Cyclodextrins (CDs) are truncated cone-shaped macrocyclic oligosaccharides consisting of a hydrophobic cavity that can include a variety of hydrophobic compounds via host–guest complexation.[6] During extensive experimentation on host–guest interactions of I–BCP–I (**3a**) as a model BCP synthon, which can be easily prepared from [1.1.1]propellane and I_2,[7] we serendipitously found that stirring an aqueous solution of α-CD and I–BCP–I at room temperature resulted in the formation of white precipitates (Figure 2A). The results of detailed titration experiments and solution/solid-state NMR studies of these water-insoluble precipitates suggested that I–BCP–I and α-CD do not form a common 1:1 host–guest threaded structure. Instead, they form a supramolecular nanocapsule structure with a 2:1 host–guest stoichiometric ratio ((α-CD)$_2$ ⊃ I–BCP–I (**5a**)) in a head-to-head (facing of secondary rims) style. Unfortunately, despite numerous attempts, we could not obtain a crystal of **5a** suitable for X-ray analysis.

Other host molecules including β-/γ-CDs, calix[*n*]arenes (*n*=4-6), pillar[*n'*]arenes (*n'*=5 and 6), or 18-crown-6-ether did not form a complex with I–BCP–I. Notably, however, the α-CD supramolecular capsule could incorporate a broad range of BCP derivatives: the corresponding ternary complexes of other 1,3-disubstituted BCPs (X–BCP–Y) such as **3b** (X = I, Y = Br), **3c** (X = I, Y = Cl), **3d** (X = I, Y = Me), **3e** (X = Br, Y = Br) and 1,3-diacetyl BCP (Ac–BCP–Ac) (**3f**) were obtained in high yields (81–95%) (Figure 2A).

Figure 2B shows the ROESY NMR spectra of (α-CD)$_2$ ⊃ I–BCP–I (**5a**) and (α-CD)$_2$ ⊃ Ac–BCP–Ac (**5f**) in D_2O solution. NOE between CH_2 of the BCP skeleton and the inner H^3 proton of the α-CD ring is clearly observed in both complexes. Moreover, in (α-CD)$_2$ ⊃ Ac–BCP–Ac (**5f**), NOE between Ac and the inner H^5 proton of the α-CD ring is also observed. These data clearly indicate the formation of an inclusion complex, in which X–BCP–Y (**3**) is accommodated in the cavity of the dimeric α-CD capsule with its substituents directed to the primary side of α-CD. Such spatial proximity between the CH_2 (**5a** and **5b**)/Br (**5b**) of BCP and inner protons of α-CD was also observed by 2D solid-state NMR of solid precipitate (Figure S1 and S2). After several attempts, we were able to obtain X-ray-grade crystals of **5f**. The complete uptake of 1 equiv. of Ac–BCP–Ac (**3f**) inside the head-to-head dimeric α-CD capsule was unambiguously demonstrated by single-crystal X-ray diffraction analysis, as shown in Figure 3. Thus, it was found that the cavity of the α-CD capsule possesses a high binding affinity for the BCP skeleton, and the dimeric encapsulation is driven by the BCP-guest. In contrast, [1.1.1]propellane (**2**) did not show host–guest complexation with α-CD, and only decomposition of propellane was observed. Silaborated BCP (Si–BCP–B) (**5g**) prepared from [1.1.1]propellane and $PhMe_2Si$–Bpin (pin = pinacolato) also did not form an inclusion complex with α-CD, presumably as a result of steric hindrance.

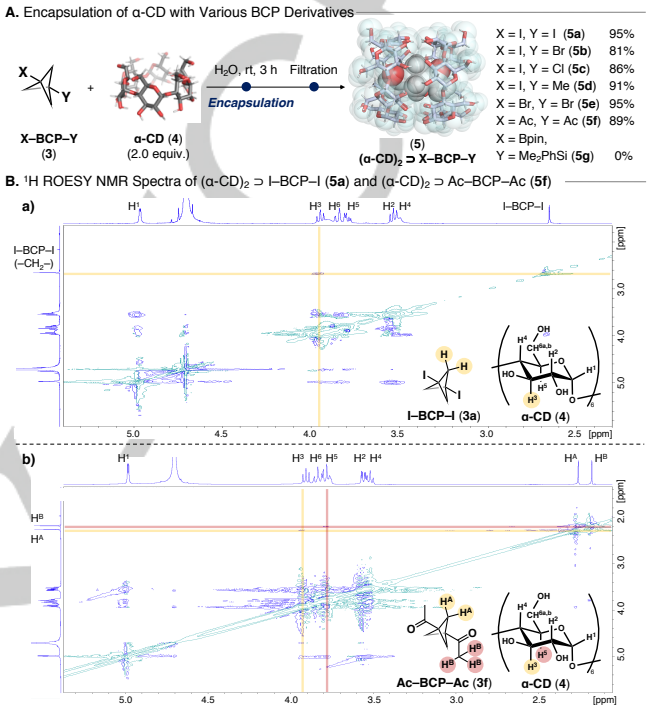


Figure 2. (A) Encapsulation of α-CD and BCP derivatives. (B) ^{1}H ROESY NMR spectra of (a) (α-CD)$_2$ ⊃ I–BCP–I (**5a**) and (b) (α-CD)$_2$ ⊃ Ac–BCP–Ac (**5f**).

Supramolecular encapsulation can change the intrinsic physicochemical properties of guest molecules. Indeed, the volatile liquid **3d** (I–BCP–Me, b.p. 37°C in 8 Torr)[8] was encapsulated within α-CD, giving (α-CD)$_2$ ⊃ I–BCP–Me (**5d**) as white microcrystals, thus making it much easier to handle. Further, sublimation is inhibited by α-CD encapsulation: the supramolecular complex (α-CD)$_2$ ⊃ Br–BCP–Br (**5e**) could be stored at 25°C for at least 7 days without decomposition or sublimation, whereas Br–BCP–Br (**3e**) itself sublimed and completely disappeared within 3 hours under the same conditions (Figure 4A). This encapsulation also greatly improves the stability of the guest BCP molecules. For example, the encapsulated (α-CD)$_2$ ⊃ I–BCP–I powder (**5a**) was thermo-, photo-, and air-stable for at least several months. Figure 4B shows the results of an evaluation of stability under ambient air and fluorescent lighting conditions by means of quantitative ^{1}H NMR analysis. No decomposition of (α-CD)$_2$ ⊃ I–BCP–I (**5a**) was detected after 65 days, which was in marked contrast to the case of I–BCP–I (**3a**) itself (ca. 100% decomposition after 65 days). Similar stabilization by encapsulation was also observed for Ac–BCP–Ac (**3f**).[9] Thus, we believe that α-CD encapsulation opens up a new horizon for the practical use of BCP synthons, greatly expanding the options for the synthesis of highly functionalized BCP molecules.

10.1002/anie.202014997

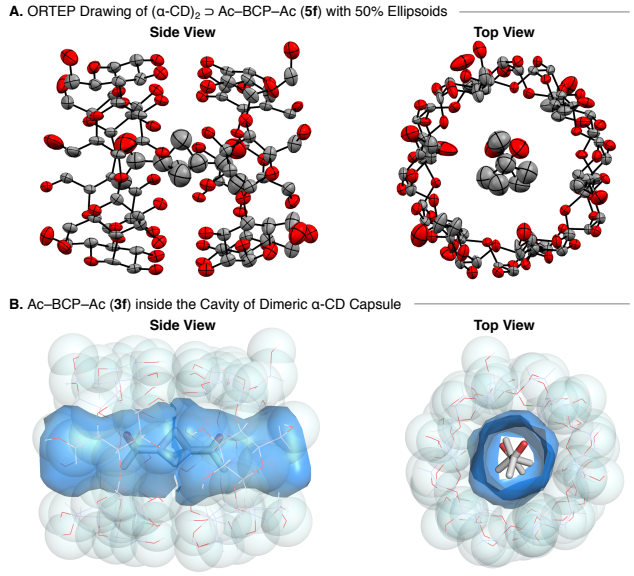


Figure 3. X-ray crystal structure of (α-CD)$_2$ ⊃Ac–BCP–Ac (**5f**). (A) All hydrogen atoms are omitted for clarity. (B) Hydrogen atoms of Ac–BCP–Ac (**3f**) are omitted for clarity.

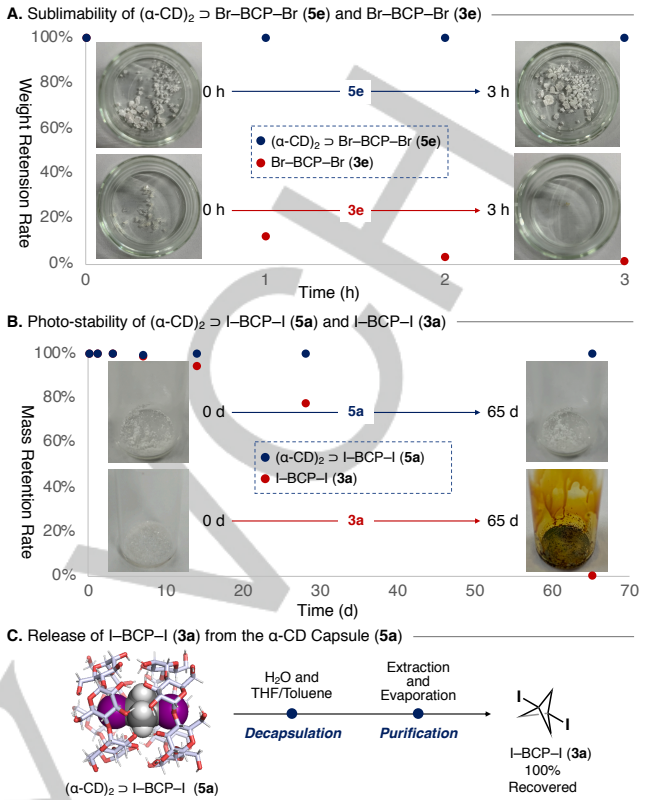


Figure 4. (A) Sublimability of (α-CD)$_2$ ⊃ Br–BCP–Br (**5e**) and Br–BCP–Br (**3e**). (B) Photo-stability of (α-CD)$_2$ ⊃ I–BCP–I (**5a**) and I–BCP–I (**3a**) (C) Release of **3a** from **5a**.

At present, the most important precursor for BCP implementation is undoubtedly [1.1.1]propellane. Thus, we examined whether α-CD capsules containing I–BCP–I complex (**5a**) can be utilized as a [1.1.1]propellane precursor. Gratifyingly, I–BCP–I (**3a**) could be recovered in 100% yield simply by stirring the α-CD inclusion capsules in toluene-THF-water and then extracting **3a** with toluene (Figure 4C). We next focused on the transformation of I–BCP–I to [1.1.1]propellane.[10] We first examined the photo-induced degradation of I–BCP–I to [1.1.1]propellane and I_2. However, the retro-reaction to regenerate I–BCP–I is rapid and barrierless,[11] and in fact, this reaction has been used to titrate [1.1.1]propellane.[12] We considered that a possible solution to this problem would be removal of I_2 from the reaction system by the use of a suitable reducing agent that can rapidly convert I_2 into I^- while leaving [1.1.1]propellane intact.

After extensive screening of various reagents, we found that anhydrous hydrazine was the best reductant for this purpose, affording [1.1.1]propellane in high yield in hexane. UV irradiation resulted in the rapid and complete formation of [1.1.1]propellane; in contrast, the reaction was sluggish under visible-light (blue LEDs) or fluorescent light irradiation at room temperature (Table S2). Notably, this reaction is not limited to hexane as the solvent, and [1.1.1]propellane solutions were obtained in comparable yields in other solvents, such as toluene, THF, and Et_2O. On the other hand, UV-sensitive solvents such as $CHCl_3$ were not compatible with these reaction conditions. Thus, we next screened a suitable nucleophile to facilitate the deiodination reaction of I–BCP–I, and we found that the combination of tributylphosphine (PBu_3) and hydrazine anhydrous promoted the elimination of I_2 from I–BCP–I without the need for UV irradiation. Other nucleophiles among those examined, such as amines and ammonium iodide salts, did not improve the reaction outcome (Table S3). In the absence of hydrazine, [1.1.1]propellane was not obtained at all.

With these two sets of optimal conditions in hand, the protocols for the preparation of [1.1.1]propellane in various solvents were optimized. Firstly, we investigated methods for the removal of hydrazine from the [1.1.1]propellane solution, and found that simple filtration with alumina drastically decreased residual hydrazine to the ppm level.[9] Consequently, non-polar (hexane, toluene) or ethereal (^{t}BuOMe, cyclopentyl methyl ether (CPME)) solutions of [1.1.1]propellane could be prepared by the UV method followed by simple filtration over alumina. For polar or other solvents such as THF, MeOH, $CHCl_3$, and MeCN, the PBu_3 method was effective, and the high-purity solutions of [1.1.1]propellane could be obtained by distillation (to remove PBu_3) and alumina filtration (to prevent hydrazine leaching). To our knowledge, this methodology is the first to enable the preparation of [1.1.1]propellane in a variety of solvents (Figure 5A).

Finally, to demonstrate the usefulness of our methods, we carried out the preparation of 1,3-diacetyl BCP (Ac–BCP–Ac; **3f**) (Figure 5B), which is an important intermediate in the synthesis of a wide range of BCP derivatives. Michl et al. developed an elegant synthetic protocol for **3f** by means of radical addition of diacetyl to [1.1.1]propellane in Et_2O under UV irradiation.[13] However, the yield is only moderate, because an ethereal solvent is unfavorable for radical reactions. We subjected a toluene solution of [1.1.1]propellane prepared by our UV method to the same diacetylation conditions, and obtained **3f** in 94% yield from (α-CD)$_2$ ⊃ Ac–BCP–Ac (**5f**).

10.1002/anie.202014997

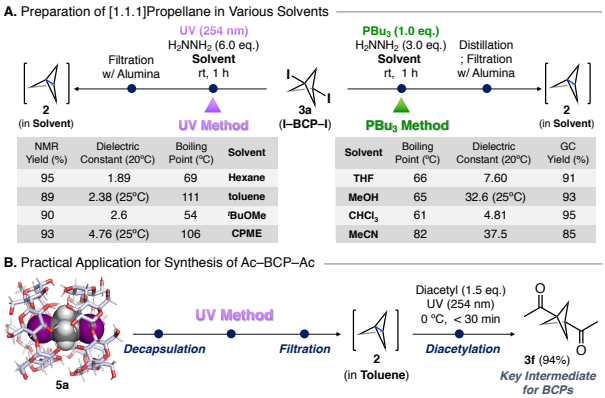


Figure 5. (A) Optimized protocols for preparation of [1.1.1]propellane. (B) Application for synthesis of Ac–BCP–Ac (**3f**) using a toluene solution of [1.1.1]propellane.

In conclusion, our α-CD encapsulation technology for BCP synthesis offers a number of important advantages: especially, (1) it avoids the issues of the intrinsic volatility, sublimability, and low boiling point of BCP derivatives, and (2) it provides a feedstock with excellent chemical, thermal, photo-, and air-stability. The encapsulated BCPs are readily generated, simply by mixing BCPs and α-CD in water, and the product is storable and easy to handle, providing a versatile synthetic platform for BCP derivatives. We also developed new protocols for deiodination reaction of 1,3-diiodo BCP (I–BCP–I) to afford [1.1.1]propellane. The combination of these technologies enables straightforward preparation of [1.1.1]propellane in a variety of solvents (protic/aprotic/polar/non-polar). We believe this will be helpful in opening up new areas of chemistry and materials science.

Acknowledgements

This work was partly supported by JSPS KAKENHI (S) (No. 17H06173) (to M.U.), JST CREST (No. JPMJCR19R2) (to M.U.), NAGASE Science Technology Development Foundation, Sumitomo Foundation, Uehara Memorial Foundation (to M.U.), JSPS KAKENHI (No. 19K23621 and 20K15950) (to J.K.), JSPS KAKENHI (C) (No. 20K05483) (to Y.N.), and JSPS KAKENHI (No. 17H03017, 18K19068, and 20H02720) (to K.M.).

Keywords: [1.1.1]propellane • bicyclo[1.1.1]pentane • α-cyclodextrin • deiodation • on-demand preparation

References

(1) (a) A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, *J. Med. Chem.* **2012**, *55*, 3414. (b) Y. P. Auberson, C. Brocklehurst, M. Furegati, T. C. Fessard, G. Koch, A. Decker, L. La Vecchia, E. Briard, *ChemMedChem* **2017**, *12*, 590. (c) N. D. Measom, K. D. Down, D. J. Hirst, C. Jamieson, E. S. Manas, V. K. Patel, D. O. Somers, *ACS Med. Chem. Lett.* **2017**, *8*, 43. (d) Y. L. Goh, Y. T. Cui, V. Pendharkar, V. A. Adsool, *ACS Med. Chem. Lett.* **2017**, *8*, 516.

(2) C. Fischer, S. L. Bogen, M. L. Childers, F. X. F. Llinas, A. J. Kim, J. W. Lampe, M. R. Machacek, D. R. Mcmasters, D. L. Jr. Parker, W. Sun, N. Sciammetta, P. P. Shao, D. L. Sloman, F. Ujjainwalla, C. Huang, International patent WO/2016/089830 A1.

(3) (a) K. Wiberg, *Chem. Rev.* **1989**, *89*, 975. (b) M. D. Levin, P. Kaszynski, J. Michl, *Chem. Rev.* **2000**, *100*, 169. (c) A. M. Dilmac, E. Spuling, A. de Meijere, S. Bräse, *Angew. Chem.* **2017**, *129*, 5778; *Angew. Chem., Int. Ed.* **2017**, *56*, 5684. (d) J. Kanazawa, M. Uchiyama, *Synlett* **2019**, *30*, 1.

(4) (a) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241. (b) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 3209. (c) J. Kanazawa, K. Maeda, M. Uchiyama, *J. Am. Chem. Soc.* **2017**, *139*, 17791. (d) I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem.* **2017**, *129*, 12949; *Angew. Chem., Int. Ed.* **2017**, *56*, 12774. (e) R. A. Shelp, P. J. Walsh, *Angew. Chem.* **2018**, *130*, 16083; *Angew. Chem., Int. Ed.* **2018**, *57*, 15857. (f) R. M. Bař, S. Kirschner, S. M. Nieger, S. Bräse, *Chem.-Eur. J.* **2018**, *24*, 1373. (g) D. F. J. Caputo, C. Arroniz, A. B. Durr, J. J. Mousseau, A. F. Stepan, S. J. Mansfield, E. A. Anderson, *Chem. Sci.* **2018**, *9*, 5295. (h) J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson, *ACS Catal.* **2019**, *9*, 9568. (i) J. M. E. Hughes, D. A. Scarlata, A. C.-Y. Chen, J. D. Burch, J. L. Gleason, *Org. Lett.* **2019**, *21*, 6800. (j) N. Trongsiriwat, Y. Pu, Y. Nieves-Quinones, R. A. Shelp, M. C. Kozlowski, P. J. Walsh, *Angew. Chem.* **2019**, *131*, 13550; *Angew. Chem., Int. Ed.* **2019**, *58*, 13416. (k) S. K. Rout, G. Marghem, J. Lan, T. Leyssens, O. A. Riant, *Chem. Commun.* **2019**, *55*, 14976. (l) X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C. MacMillan, *Nature* **2020**, *580*, 220. (m) M. Kondo, J. Kanazawa, T. Ichikawa, T. Shimokawa, Y. Nagashima, K. Miyamoto, M. Uchiyama, *Angew. Chem.* **2020**, *132*, 1986; *Angew. Chem., Int. Ed.* **2020**, *59*, 1970. (n) S. Yu, C. Jing, A. Noble, V. K. Aggarwal, *Angew. Chem.* **2020**, *132*, 3945; *Angew. Chem., Int. Ed.* **2020**, *59*, 3917. (o) J. H. Kim, A. Ruffoni, Y. S. S. Al-Faiyz, N. S. Sheikh, D. Leonori, *Angew. Chem.* **2020**, *132*, 8302; *Angew. Chem., Int. Ed.* **2020**, *59*, 8225. (p) K. Schwärzer, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem.* **2020**, *132*, 20412; *Angew. Chem., Int. Ed.* **2020**, *59*, 20235.

(5) K. Semmler, G. Szeimies, J. Belzner, *J. Am. Chem. Soc.* **1985**, *107*, 6410.

(6) (a) K. A. Connors, *Chem. Rev.* **1997**, *97*, 1325. (b) M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875. (c) G. Crini, *Chem. Rev.* **2014**, *114*, 10940.

(7) K. B. Wiberg, S. T. Waddell, K. Laidig, *Tetrahedron Lett.* **1986**, *27*, 1553.

(8) N. S. Zefirov, L. S. Surmina, N. K. Sadovaya, A. V. Blokhin, M. A. Tyurekhodzhaeva, Y. N. Bubnov, L. I. Lavrinovich, A. V. Ignatenko, Y. K. Grishin, O. A. Zelenkina, N. G. Kolotyrkina, S. V. Kudrevich, A. S. Koz'min, *Zh. Org. Khim.* **1990**, *26*, 2317.

(9) For details, see Supporting Information.

(10) Alber and Szeirnies reported that solvent-free [1.1.1]propellane could be prepared from I–BCP–I (**3a**) by using sodium cyanide in DMSO. For details, see: F. Alber, G. Szeimies, *Chem. Ber.* **1992**, *125*, 757.

(11) A. J. Sterling, A. B. Dürr, R. C. Smith, E. A. Anderson, F. Duarte, *Chem. Sci.* **2020**, *11*, 4895.

(12) K. R. Mondanaro, W. P. Dailey, *Org. Synth.* **1998**, *75*, 98.

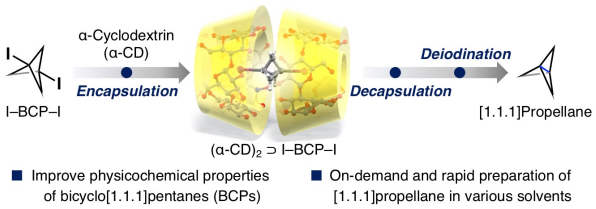
(13) P. Kaszynski, J. Michl, *J. Org. Chem.* **1988**, *53*, 4593.

10.1002/anie.202014997

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents



α-Cyclodextrin (α-CD) encapsulation of bicyclo[1.1.1]pentane (BCP) derivatives could provide a bench-top-storable format for BCP derivatives. Furthermore, simple protocols for deiodination reaction of 1,3-diiodo BCP were developed to afford [1.1.1]propellane. Together, these findings provided novel and 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.