Natural Product Synthesis

International Edition: DOI: 10.1002/anie.201604102
German Edition: DOI: 10.1002/ange.201604102

A Synthesis of (±)-Aplydactone

*Robin Meier and Dirk Trauner**

Dedicated to Professor Samuel J. Danishefsky on the occasion of his 80th birthday

Abstract: *Aplydactone is an unusual brominated sesquiterpenoid isolated from the sea hare Aplysia dactylomela. Its highly strained skeleton contains two four- and three six-membered rings and features three adjacent quaternary carbon atoms. Although it is most likely of photochemical origin, attempts to generate it from a chamigrane precursor have failed thus far. In this work, we present a total synthesis of aplydactone that relies on two photochemical key steps that are not biomimetic but highly effective in establishing the two cyclobutane rings. Our synthesis also features an unusual Barbier-type cyclization and culminates in new radical conditions to install the sterically hindered secondary bromide of the natural product.*

Photochemical steps are rare in biosynthesis but can give rise to natural products with unusual architectures.[1] They seem to be especially relevant in organisms that live in shallow seawater and at latitudes where solar irradiation is comparatively intense.[2]

In 2001, Stonik and co-workers reported the isolation of aplydactone (**1**), an intriguing cyclobutane-containing natural product, from *Aplysia dactylomela* (Figure 1).[3] This sea hare also produces dactylone (**2**) and the brominated chamigranes **3** and **4**.[4] The biological specimens were collected at a water depth of 3–5 m at the northern coast of Madagascar. Therefore, it is reasonable to assume that the cyclobutane rings in **1** are formed from **2** by intramolecular photochemical [2+2] cycloaddition.[5] Nevertheless, Stonik et al. reported that **2** could not be converted into **1** under "long-term UV irradiation".[3] Although this result is worthy of revisiting using modern theoretical and photochemical methods, we decided to explore alternative approaches to synthesize **1**.

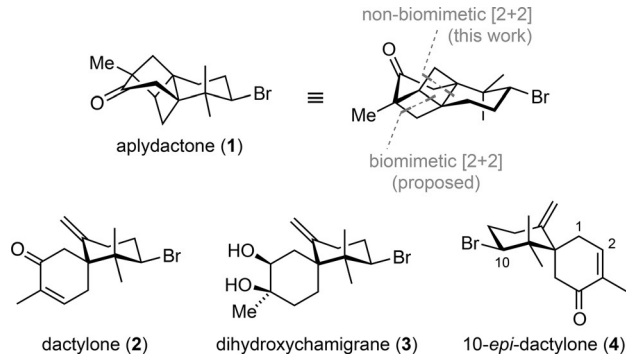


Figure 1. Aplydactone (**1**) and the brominated chamigranes **2**–**4**, isolated from the sea hare *Aplysia dactylomela*.

From a synthetic point of view, the polycyclic structure of **1** provides a considerable challenge owing to the high ring strain and steric congestion of the unique tetracyclo[4.4.2.0^{1,6}.0^{3,11}]dodecane skeleton. This framework features an unprecedented [2]-ladderane moiety,[6] which is connected to a *cis*-decalin system comprising four quaternary centers and a secondary neopentyl bromide. As a result of this bridged core structure, the bond lengths and angles within the four-membered rings are highly distorted from the usual values of puckered cyclobutanes. Indeed, aplydactone (**1**) readily undergoes a Wagner–Meerwein rearrangement under acidic conditions to relieve ring strain.[3]

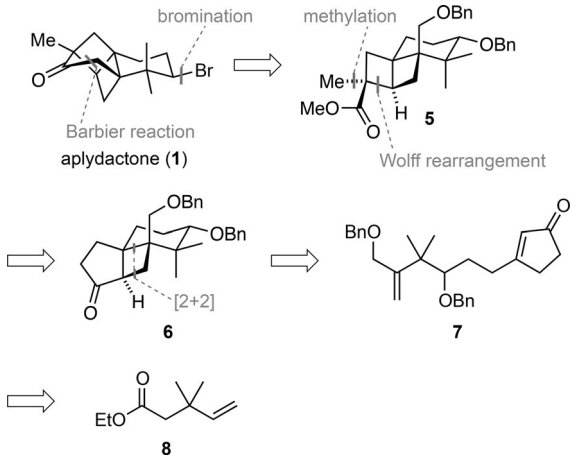
To the best of our knowledge, just one synthetic study towards **1** has been reported despite its intriguing structure.[7] Herein, we disclose the first total synthesis of aplydactone (**1**), which hinges on photochemical transformations.

A survey of the literature suggested that either a [2+2] cycloaddition of a transient cyclobutadiene[6,8] or a contraction of a bicyclo[3.2.0]heptane ring system[6,8d,9] would be most suitable for the establishment of the central bicyclo[2.2.0]hexane moiety of aplydactone (**1**). As cyclobutadiene cycloaddition proved to be non-viable, we based our retrosynthetic analysis on a photochemical [2+2] cycloaddition and a ring contraction (Scheme 1). Late-stage bromination and disconnection of one of the six-membered rings would suggest **5** as a suitable intermediate, which could be traced back to **6** by a Wolff ring contraction and methylation. Furthermore, we rationalized that intermediate **6** could be prepared in one step through an intramolecular [2+2] photocycloaddition from cyclopentenone **7**, which can be derived from known ester **8**.

Our actual synthesis began with the preparation of alkyl bromide **10** starting from known ester **8**, which was prepared on decagram scale by a Johnson–Claisen rearrangement (Scheme 2).[10] A reaction sequence involving ozonolysis,[10b] allylation[11] with subsequent lactonization, a second ozonolysis with full reduction, and protection afforded lactone **9**. Methenylation,[12] reduction, and double benzylation of lactone **9** were followed by selective deprotection of the SEM group[13] and bromination to obtain **10**. This opening sequence was scalable and provided bromide **10** from ester **8** in 43% overall yield on multigram scale. For the installation

[*] R. Meier, Prof. Dr. D. Trauner
Department of Chemistry
Ludwig-Maximilians-Universität München
81377 Munich (Germany)
E-mail: dirk.trauner@lmu.de

Supporting information and the ORCID identification numbers for the authors of this article can be found under http://dx.doi.org/10.1002/anie.201604102.

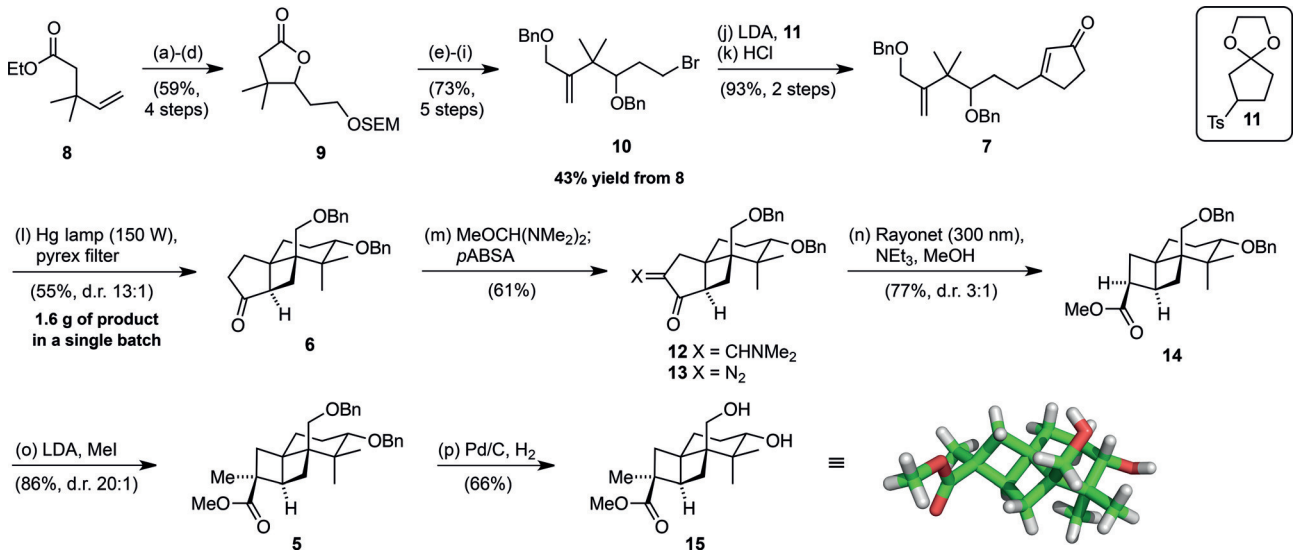


Scheme 1. Retrosynthetic analysis of aplydactone (**1**).

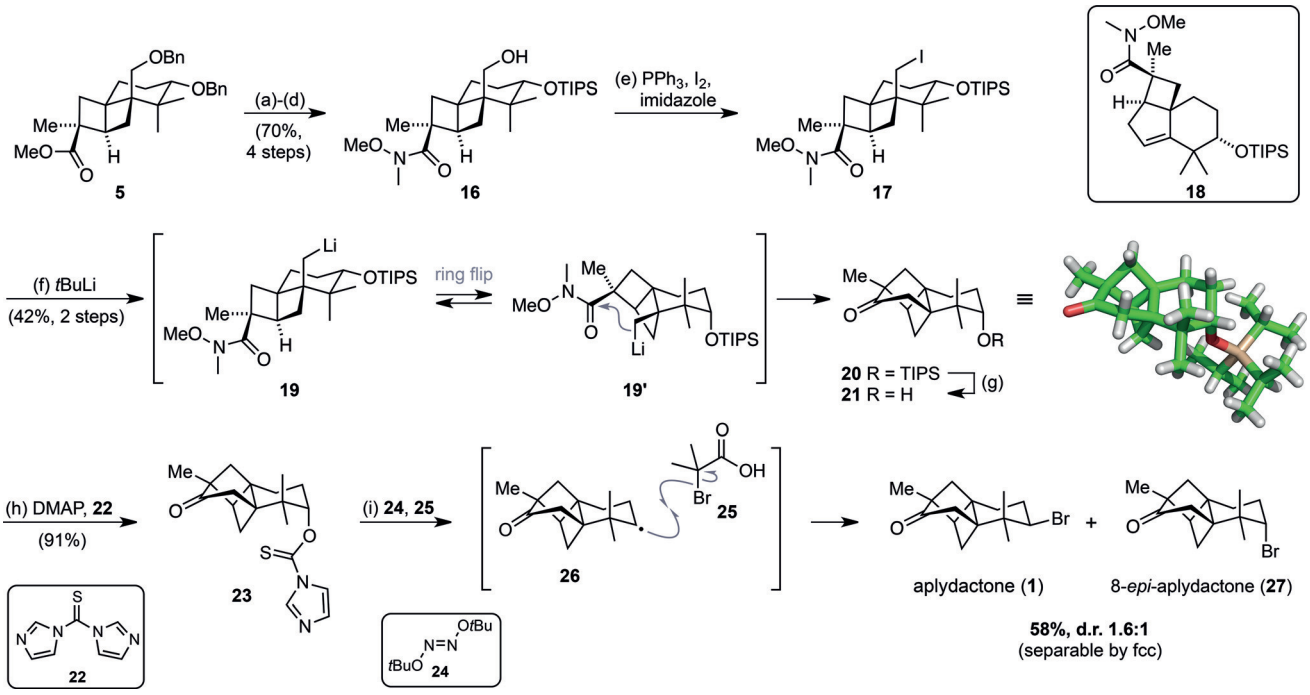
of the cyclopentenone moiety, we used a method introduced by Yoshida and Saito.[14] Coupling of sulfone **11** with bromide **10** followed by acid-induced deprotection and elimination gave precursor **7** in excellent yield. With gram quantities of **7** in hand, we turned our attention to the photochemical [2+2] cycloaddition, which needed to build up two quaternary stereocenters next to a sterically hindered *gem*-dimethyl moiety.[5b,15] After some optimization, key intermediate **6** could be obtained in decent yield and very good diastereoselectivity upon irradiation of **7** with UV light. The relative configuration of the complex ring system was established by NOESY experiments.

To establish the ladderane motif of aplydactone (**1**), the cyclopentanone ring of **6** had to be contracted. To our surprise, the formation of α-diazo ketone **13** turned out to be more challenging than expected. Activation of **6** through formylation[16] or trifluoroacetoxylation[17] followed by diazo transfer as well as direct-transfer conditions[18] suffered from low yield. However, **13** could be prepared by treatment of enaminone **12** with *p*ABSA.[9a,19] The subsequent photochemical Wolff rearrangement[20] proceeded smoothly and provided ladderane **14** in good yield as a 3:1 diastereomeric mixture (major diastereomer shown). Following deprotonation, methylation occurred from the less hindered face of the bicyclo[2.2.0]hexane scaffold generating ester **5**, which features all requisite quaternary stereocenters, in very good yield. The structure of **5** was established by NOESY experiments and was ultimately confirmed by X-ray structure analysis of diol **15**, which was obtained by double debenzylation.

The next phase of our synthesis required the closure of the six-membered ring to obtain the full carbon skeleton of **1**. Whereas selective functionalization of the primary neopentyl alcohol was not feasible, we were able to selectively deprotect the secondary alcohol of **5** under reductive conditions (Scheme 3). Reprotection as a silyl ether and deprotection of the primary alcohol followed by conversion of the ester into the Weinreb amide gave **16**. Iodination of **16** under Garegg–Samuelsson conditions[21] produced the highly sensitive iodide **17**, which readily rearranged to cyclopentene **18**.[22] Conducting the reaction and the quenching at low temperature suppressed the ring expansion and provided the desired iodide **17** as the major reaction product. Treatment of iodide



Scheme 2. Synthesis of key intermediate **5**. a) O_3, CH_2Cl_2/MeOH, −78 °C; then PPh_3, −78 °C→RT, 95%; b) Zn, allyl bromide, THF, 0 °C→RT, 78%; c) O_3, CH_2Cl_2/MeOH, −78 °C; then PPh_3, −78 °C→RT; then $NaBH_4$, 0 °C→RT; d) SEMCl, DIPEA, CH_2Cl_2, 0 °C→RT, 80% over 2 steps; e) LHMDS, $CH_2NMe_2^+I^-$, THF, −78 °C→RT; then MeI, MeOH, 0 °C→RT; then DBU, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C→RT, 92%; f) DIBAL-H, THF, 0 °C→RT, 94%; g) NaH, BnBr, TBAI, THF, 0 °C→50 °C, 90%; h) *n*BuSH, $MgBr_2{\cdot}OEt_2$, K_2CO_3, Et_2O, RT, quant.; i) PPh_3, NBS, CH_2Cl_2, 0 °C→RT, 94%; j) **11**, LDA, THF, −78 °C; then **10**, −78 °C→RT; k) HCl, THF, 60 °C, 93% over 2 steps; l) medium-pressure Hg lamp (150 W), pyrex filter, EtOAc, −78 °C, 55% (13:1 d.r.); m) $MeOCH(NMe_2)_2$, THF, N_2 stream (open flask), 60 °C; then *p*ABSA, dioxane, 70 °C, 61%; n) NEt_3, Rayonet lamp (300 nm), MeOH, RT, 77% (3:1 d.r.); o) LDA, THF, −78 °C; then MeI, −78 °C→−50 °C, 86% (20:1 d.r.); p) Pd/C, H_2 (1 atm), MeOH, RT, 66%. Bn = benzyl, DIBAL-H = diisobutylaluminum hydride, DIPEA = diisopropylethylamine, LDA = lithium diisopropylamide, LHMDS = lithium hexamethyldisilazide, NBS = *N*-bromosuccinimide, *p*ABSA = 4-acetamidobenzenesulfonyl azide, SEMCl = [2-(trimethylsilyl)ethoxy]methyl chloride, TBAI = tetra-*n*-butylammonium iodide, Ts = *para*-toluenesulfonyl.[30]



Scheme 3. Completion of the synthesis of aplydactone (**1**). a) Pd/C, H_2 (1 atm), EtOH, RT; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 83 % over 2 steps; c) $Pd(OH)_2$, H_2 (1 atm), MeOH, RT, 97 %; d) LHMDS, $Me(OMe)NH_2Cl$, THF, −78 °C→0 °C, 87 %; e) PPh_3, I_2, imidazole, CH_2Cl_2, −20 °C→−15 °C; f) *t*BuLi (reverse addition), pentane/Et_2O, −115 °C→−60 °C, 42 % over 2 steps; g) TBAF, THF, 0 °C→RT, 91 %; h) **22**, DMAP, THF, 60 °C, 91 %; i) **24** (4 equiv, syringe pump), **25** (5 equiv), benzene, 60 °C, 58 % (1.6:1 d.r.). DMAP = 4-(dimethylamino)pyridine, TBAF = tetra-*n*-butylammonium fluoride, TIPSOTf = triisopropylsilyl trifluoromethanesulfonate.[30]

17 with 2.2 equiv *t*BuLi at −115 °C in an ether/pentane solvent mixture afforded the desired ketone **20** in 42 % overall yield from **16**.[23] This unusual ring closure warrants further analysis. Under the chosen conditions, first organolithium species **19** should form via an ionic ate complex,[24] thus preventing a radical ring opening or expansion.[25] Subsequently, **19** must undergo a substantial conformational rearrangement (**19**→**19′**) to bring the nucleophilic site into close proximity to the electrophilic Weinreb amide. This rearrangement entails an inversion of the cyclohexane ring that brings the silyl-protected alcohol into an axial position. The resulting conformation is clearly visible in the crystal structure of product **20**, which already possesses the full carbon skeleton of aplydactone (**1**). Subsequent silyl deprotection with TBAF afforded alcohol **21**.

Unsurprisingly, attempts to convert activated derivatives of the secondary neopentyl alcohol into the desired bromide by nucleophilic displacement were unsuccessful owing to steric hindrance.[26] This prompted us to seek radical bromination conditions as an alternative method for the final C–Br bond formation. The conversion of alcohols and their derivatives into alkyl halides under radical conditions has been rarely explored, and the known methods failed in our hands.[27] Therefore, we decided to develop new conditions for this transformation based on the work of Zard et al. on the conversion of *S*-alkyl-*O*-ethyl xanthates into alkyl bromides.[28] To this end, alcohol **21** was converted into the corresponding imidazole **23**. Slow addition of di-*tert*-butyl hyponitrite (**24**)[29] to a solution of **23** and α-bromo acid **25** led to the formation of radical **26**, which abstracted a bromine atom from **25** to afford aplydactone (**1**) and its C8 epimer **27** in 36 % and 22 % yield, respectively. The applied combination of radical initiator and bromine source was essential for the success of this transformation. Di-*tert*-butyl hyponitrite (**24**) enabled low-temperature initiation, thereby preventing competitive thermal elimination of the thiocarbonylimidazole. Furthermore, α-bromo acid **25** showed better reactivity than bromotrichloromethane and was more easily removed from the reaction mixture than α-bromo esters and malonates. The two epimers **1** and **27** were separable by standard flash column chromatography, and the analytical data of synthetic **1** were in full accordance with those reported for the isolated natural product. Incidentally, 8-*epi*-aplydactone (**27**) may emerge as a natural product arising from the photocycloaddition of 10-*epi*-dactylone (**4**), which was isolated together with dactylone (**2**) and aplydactone (**1**) from *Aplysia dactylomela*.

In summary, we have achieved the first total synthesis of the unusual brominated sesquiterpenoid aplydactone (**1**) in racemic form. Our approach relies on two non-biomimetic photoreactions to construct the [2]-ladderane scaffold. An initial diastereoselective [2+2] cycloaddition generated the three adjacent quaternary centers present in the natural product. A photochemical Wolff rearrangement followed by late-stage Barbier-type ring closure provided the core structure of **1**. New reaction conditions were developed for the radical conversion of a sterically hindered thiocarbonylimidazole into an alkyl bromide to complete the synthesis. Further investigations on the substrate scope of this reaction and the biosynthesis of **1** are underway.

Acknowledgements

We thank the Center for Integrated Protein Science Munich (CIPSM) for financial support. We would like to acknowledge Prof. Dr. Thorsten Bach and his co-workers Dr. Andreas Bauer and Christoph Brenninger for technical support and helpful discussions regarding the photochemistry. Furthermore, Dr. Nicolas Armanino and Dr. Bryan Matsuura are acknowledged for helpful discussions and excellent support with the preparation of this manuscript.

Keywords: cycloaddition · halogenation · natural products · photochemistry · radical reactions

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 11251–11255
Angew. Chem. **2016**, *128*, 11418–11422

[1] For selected examples, see: a) S. A. Look, W. Fenical, D. Van Engen, J. Clardy, *J. Am. Chem. Soc.* **1984**, *106*, 5026–5027; b) R. G. S. Berlinck, R. Britton, E. Piers, L. Lim, M. Roberge, R. Moreira da Rocha, R. J. Andersen, *J. Org. Chem.* **1998**, *63*, 9850–9856; c) I. K. Mangion, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3696–3697; d) K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe, D. R. Burton, *J. Am. Chem. Soc.* **2008**, *130*, 11114–11121; e) G. Majetich, J. Yu, *Org. Lett.* **2008**, *10*, 89–91; f) B.-X. Zhao, Y. Wang, C. Li, G.-C. Wang, X.-J. Huang, C.-L. Fan, Q.-M. Li, H.-J. Zhu, W.-M. Chen, W.-C. Ye, *Tetrahedron Lett.* **2013**, *54*, 4708–4711.

[2] For selected examples, see: a) C. Ireland, J. Faulkner, *Tetrahedron* **1981**, *37*, 233–240; b) S. J. Eade, M. W. Walter, C. Byrne, B. Odell, R. Rodriguez, J. E. Baldwin, R. M. Adlington, J. E. Moses, *J. Org. Chem.* **2008**, *73*, 4830–4839; c) S.-J. Piao, Y.-L. Song, W.-H. Jiao, F. Yang, X.-F. Liu, W.-S. Chen, B.-N. Han, H.-W. Lin, *Org. Lett.* **2013**, *15*, 3526–3529; d) D. Stichnoth, P. Kölle, T. J. Kimbrough, E. Riedle, R. de Vivie-Riedle, D. Trauner, *Nat. Commun.* **2014**, *5*, 5597.

[3] S. N. Fedorov, O. S. Radchenko, L. K. Shubina, A. I. Kalinovsky, A. V. Gerasimenko, D. Y. Popov, V. A. Stonik, *J. Am. Chem. Soc.* **2001**, *123*, 504–505.

[4] a) S. N. Fedorov, M. V. Reshetnyak, A. P. Schedrin, S. G. Ilyin, J. T. Struchkov, V. A. Stonik, G. B. Elyakov, *Dokl. Akad. Nauk SSSR* **1990**, *307*, 877–879; b) L. K. Shubina, S. N. Fedorov, A. I. Kalinovskiy, A. S. Dmitrenok, J. O. Jin, M. G. Song, J. Y. Kwak, V. A. Stonik, *Russ. Chem. Bull.* **2007**, *56*, 2109–2114.

[5] a) J. Iriondo-Alberdi, M. F. Greaney, *Eur. J. Org. Chem.* **2007**, 4801–4815; b) T. Bach, J. P. Hehn, *Angew. Chem. Int. Ed.* **2011**, *50*, 1000–1045; *Angew. Chem.* **2011**, *123*, 1032–1077; c) Y. J. Hong, D. J. Tantillo, *Chem. Soc. Rev.* **2014**, *43*, 5042–5050; for a related [2+2] photocycloadduct, see: d) J. Bordner, L. R. Morrow, *Cryst. Struct. Commun.* **1976**, *5*, 523–526.

[6] D. H. Nouri, D. J. Tantillo, *Curr. Org. Chem.* **2006**, *10*, 2055–2074.

[7] J. M. Rohde, Ph.D. Thesis, The Scripps Research Institute, La Jolla, California, **2005**.

[8] a) J. C. Barborak, L. Watts, R. Pettit, *J. Am. Chem. Soc.* **1966**, *88*, 1328–1329; b) J. A. Tallarico, M. L. Randall, M. L. Snapper, *J. Am. Chem. Soc.* **1996**, *118*, 9196–9197; c) J. Limanto, J. A. Tallarico, J. R. Porter, K. S. Khuong, K. N. Houk, M. L. Snapper, *J. Am. Chem. Soc.* **2002**, *124*, 14748–14758; for a review on this topic, see: d) H. Hopf, *Angew. Chem. Int. Ed.* **2003**, *42*, 2822–2825; *Angew. Chem.* **2003**, *115*, 2928–2931.

[9] a) K. B. Wiberg, B. L. Furtek, L. K. Olli, *J. Am. Chem. Soc.* **1979**, *101*, 7675–7679; b) W. G. Dauben, D. M. Walker, *Tetrahedron Lett.* **1982**, *23*, 711–714; c) V. B. Rao, S. Wolff, W. C. Agosta, *J. Chem. Soc. Chem. Commun.* **1984**, 293–294; d) V. Mascitti, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 15664–15665; e) V. Mascitti, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 3118–3119.

[10] a) W. A. Kleschick, *J. Org. Chem.* **1986**, *51*, 5429–5433; b) L. Carman, L. D. Kwart, T. Hudlicky, *Synth. Commun.* **1986**, *16*, 169–182.

[11] a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293; b) B. C. Ranu, A. Majee, A. R. Das, *Tetrahedron Lett.* **1995**, *36*, 4885–4888.

[12] J. L. Roberts, P. S. Borromeo, C. D. Poulter, *Tetrahedron Lett.* **1977**, *18*, 1621–1623.

[13] S. Kim, I. S. Kee, Y. H. Park, J. H. Park, *Synlett* **1991**, 183–184.

[14] a) T. Yoshida, S. Saito, *Chem. Lett.* **1982**, *11*, 165–168; b) T. Yoshida, S. Saito, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3931–3932.

[15] a) M. T. Crimmins, *Chem. Rev.* **1988**, *88*, 1453–1473; b) M. T. Crimmins, P. S. Watson, *Tetrahedron Lett.* **1993**, *34*, 199–202; c) M. T. Crimmins, S. Huang, L. E. Guise-Zawacki, *Tetrahedron Lett.* **1996**, *37*, 6519–6522; d) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052–1103; e) J. P. Hehn, C. Müller, T. Bach in *Handbook of Synthetic Photochemistry* (Eds.: A. Albini, M. Fagnoni), Wiley-VCH, **2010**, pp. 171–215; f) S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.5b00723.

[16] M. Regitz, J. Rüter, *Chem. Ber.* **1968**, *101*, 1263–1270.

[17] R. L. Danheiser, R. F. Miller, R. G. Brisbois, S. Z. Park, *J. Org. Chem.* **1990**, *55*, 1959–1964.

[18] a) L. Lombardo, L. N. Mander, *Synthesis* **1980**, 368–369; b) T. Uyehara, N. Takehara, M. Ueno, T. Sato, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2687–2694.

[19] a) M. Regitz, G. Himbert, *Justus Liebigs Ann. Chem.* **1970**, *734*, 70–85; b) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160; c) G. Maas, *Angew. Chem. Int. Ed.* **2009**, *48*, 8186–8195; *Angew. Chem.* **2009**, *121*, 8332–8341; d) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981–10080.

[20] W. Kirmse, *Eur. J. Org. Chem.* **2002**, 2193–2256.

[21] a) P. J. Garegg, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866–2869; b) P. J. Garegg, R. Johansson, C. Ortega, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1982**, 681–683.

[22] For the use of cyclobutane fragmentation in organic synthesis, see: a) J. D. Winkler, C. M. Bowen, F. Liotta, *Chem. Rev.* **1995**, *95*, 2003–2020; b) J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485–1538.

[23] For selected examples, see: a) T. van der Does, G. H. Klumpp, M. Schakel, *Tetrahedron Lett.* **1986**, *27*, 519–520; b) D. Kim, Y. K. Lee, *Tetrahedron Lett.* **1991**, *32*, 6885–6886; c) I. S. Aidhen, J. R. Ahuja, *Tetrahedron Lett.* **1992**, *33*, 5431–5432; d) A. M. Baylis, M. P. H. Davies, E. J. Thomas, *Org. Biomol. Chem.* **2007**, *5*, 3139–3155; e) T. Burns, M. Helliwell, E. J. Thomas, *Tetrahedron Lett.* **2013**, *54*, 2120–2123.

[24] a) K. B. Wiberg, S. Sklenak, W. F. Bailey, *J. Org. Chem.* **2000**, *65*, 2014–2021; b) W. F. Bailey, J. D. Brubaker, K. P. Jordan, *J. Organomet. Chem.* **2003**, *681*, 210–214.

[25] For selected examples of cyclobutylcarbinyl radical fragmentation, see: a) F. E. Ziegler, R. X. Kover, N. N. K. Yee, *Tetrahedron Lett.* **2000**, *41*, 5155–5159; b) W. D. Shipe, E. J. Sorensen, *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035; c) J. P. Hehn, M. Kemmler, T. Bach, *Synlett* **2009**, 1281–1284; d) J. P. Hehn, E. Herdtweck, T. Bach, *Org. Lett.* **2011**, *13*, 1892–1895; e) J. Shi, S.-S. Chong, Y. Fu, Q.-X. Guo, L. Liu, *J. Org. Chem.* **2008**, *73*, 974–982.

[26] a) A. Fukuzawa, H. Sato, T. Masamune, *Tetrahedron Lett.* **1987**, *28*, 4303–4306; b) V. Bhat, J. A. MacKay, V. H. Rawal, *Tetrahedron* **2011**, *67*, 10097–10104; c) V. Bhat, V. H. Rawal, *Chem. Commun.* **2011**, *47*, 9705–9707; d) W.-J. Chung, C. D. Vanderwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 4396–4434; *Angew. Chem.* **2016**, *128*, 4470–4510.

[27] a) F. R. Jensen, T. I. Moder, *J. Am. Chem. Soc.* **1975**, *97*, 2281–2283; b) S. J. Cristol, D. G. Seapy, *J. Org. Chem.* **1982**, *47*, 132–

136; c) D. Crich, S. M. Fortt, *Synthesis* **1987**, 35 – 37; d) W. Damm, B. Giese, J. Hartung, T. Hasskerl, K. N. Houk, O. Hueter, H. Zipse, *J. Am. Chem. Soc.* **1992**, *114*, 4067 – 4079; e) B. Giese, J. Hartung, *Chem. Ber.* **1992**, *125*, 1777 – 1779; for the hydrobromination of alkenes by hydrogen-atom transfer, see: f) X. Ma, S. B. Herzon, *Chem. Sci.* **2015**, *6*, 6250 – 6255.

[28] F. Barbier, F. Pautrat, B. Quiclet-Sire, S. Z. Zard, *Synlett* **2002**, 811 – 813.

[29] For the preparation of **24**, see: a) G. D. Mendenhall, *Tetrahedron Lett.* **1983**, *24*, 451 – 452; b) J. T. Banks, J. C. Scaiano, W. Adam, R. S. Oestrich, *J. Am. Chem. Soc.* **1993**, *115*, 2473 – 2477.

[30] CCDC 1475334 (**15**) and 1475333 (**20**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: April 27, 2016
Published online: June 30, 2016

