Cascade Reactions

Photochemical Approach to the Cyclohepta[*b*]indole Scaffold by Annulative Two-Carbon Ring-Expansion

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Abstract: We report on the implementation of the concept of a photochemically elicited two-carbon homologation of a π-donor–π-acceptor substituted chromophore by triple-bond insertion. Implementing a phenyl connector between the slide-in module and the chromophore enabled the synthesis of cyloheptа[*b*]indole-type building blocks by a metal-free annulative one-pot two-carbon ring expansion of the five-membered chromophore. Post-irradiative structural elaboration provided founding members of the indolo[2,3-*d*]tropone family of compounds. Control experiments in combination with computational chemistry on this multibond reorganization process founded the basis for a mechanistic hypothesis.

The *N*-heteroacene cyclohepta[*b*]indol[1] (**1**) features the basic scaffold of a variety of man-made pharmaceutically active compounds[2] and natural products,[3] for example, alstonlarsine A (**2**)[4] (Figure 1). To address the challenges associated with the synthesis of cyclohepta[*b*]indol-type building blocks, a well-diversified portfolio of enabling synthetic methods is already available.[5] Variations of annulation reactions,[6] of (*m*+*n*)-cycloadditions,[7] and of the Cope rearrangement[8] have proven particularly valuable. Notably, however, organic photochemistry has not yet been exploited to access perhydrocyclohepta[*b*]indole-type building blocks (**3**).

To complement the existing methodology, we aimed for a *fuse–compress–expand* sequence to 6,7-dihydro-cyclohepta[*b*]indol-8(5*H*)-ones **4** that exploits an unprecedented photochemically triggered two-carbon ring-expansion (Figure 2).[9] *Fusing* is accomplished by Sonogashira cross-coupling between *o*-iodo anilines (**5**) and terminal alkynes (**6**), followed by condensation with five-membered cyclic 1,3-dicarbonyl compounds (**7**) and finalized by *N*-acylation to deliver photochemistry-competent vinylogous amides **8**. The subsequent *compress*-and-*expand* phase consists of a photochemically triggered formation of a transient [2+2]-cycloadduct that subsequently collapses to deliver the 6,7-dihydro-cyclohepta[*b*]indol-8(5*H*)-one **4**; hence, the actual ring-expansion merges excited-state with ground state chemistry to an unprecedented one-pot process.

The experimental procedures and characterization data for the products **8** of the *fuse*-phase are provided in full detail in the Supporting Information (29 examples). The results of our study on the photochemically triggered two-carbon ring-expansion of **8** are summarized in Tables 1–3. We adopted our previously optimized conditions for the alkyne de Mayo reaction without the necessity of optimization. Hence, solutions of the *N*-protected vinylogous amides **8a**–**ab** (0.16 mmol) in degassed 2,2,2-trifluoroethanol (TFE, $c = 0.03$ M) were irradiated in sealable quartz tubes using the low-pressure mercury vapor lamps ($E_{max} = 254$ nm) of a commercially available photoreactor. Reaction times refer to reactor running times. The appearance

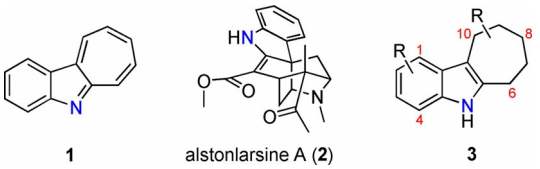

Figure 1. Motif (**1**), Variation (**2**), and Building Block (**3**).

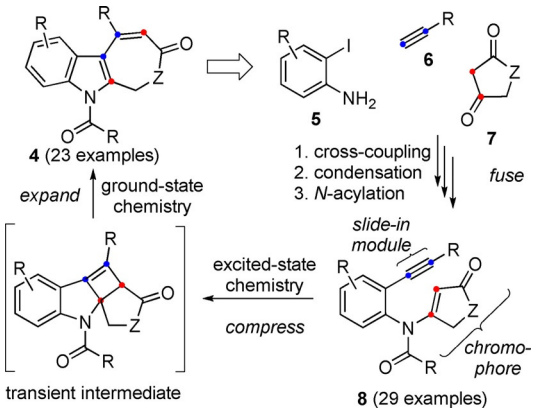

Figure 2. *Fuse–compress–expand* strategy to 6,7-dihydrocyclohepta[*b*]indol-8(5*H*)-ones.

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of yellow colored reaction mixtures served as an indicator for product formation and progression of conversion was detected by TLC analysis.

Representative examples for aliphatic and aromatic substituents at C-10 were initially screened (Table 1). Ring expansion proceeded for R^1 = octyl- (**8a**), 4-hydroxylbutyl- (**8b**) and 4-siloxybutyl (**8c**) to deliver **4a**–**c** in useful yields (85–92%). Somewhat unexpectedly, hydroxylmethyl-substitution (**8d**) triggered decomposition under irradiation. No defined degradation product could be isolated. The nature of the decomposition pathway(s) remains speculative. Fortunately, irradiation of the corresponding silyl ether **8e** delivered the ring-expansion product **4e** in 86% yield. 2-Aminotolane-derived **8f** was susceptible to ring-expansion at prolonged reaction times and delivered the R^1 = phenyl substituted **4f** in moderate yield (52%).

For pharmaceutically relevant cyclohepta[*b*]indoloids, substituent diversification at C-2 is frequently found.[2] Consequently, we moved on to study substituent effects for $R^2 \neq H$ at C-2 and using $R^1 = CH_3$ at C-10 as a prototype for alkyl substitution (Table 2). Methyl- (**8g**), trifluoromethyl- (**8h**) and *tert-butyl*-substitution (**8i**) at C-2 were tolerated and **4g-i** were isolated in valuable yields (75–91%). 4-Aminobiphenyl-based **8j** underwent the ring-expansion slowly and sluggishly to provide **4j** (26%) in low yield. Bromo or fluoro substitution enabled access to **4k** (83%) or **4l** (83%). Suzuki–Miyaura cross-coupling of **4k** with phenylboronic acid under carefully optimized conditions delivered **4j** (92%); thus **4k** may serve as a relay compound for post-ring expansion structural diversification (vide infra).[10] π-Donor ($R^2 = OCH_3$) and π-acceptor ($R^2 = CO_2Me$ or CN) substitution allowed the formation of **4m** (57%), **4n** (86%), and **4o** (86%). However, no conversion was observed for $R^2 = NO_2$ (**8p**, not depicted).

We proceeded to study substituent effects at C-3 or C-4 for $R^2 = H$ at C-2 and $R^1 = CH_3$ at C-10. (Table 3). Subjecting vinylogous amides featuring methyl (**8q**), fluoro (**8r**), or chloro (**8s**) substitution at C-3 to the ring-expansion protocol afforded **4q** (90%), **4r** (83%), and **4s** (86%) in valuable yields. Ring-expan-

Table 1. Two-carbon ring expansion: Varying R^1.

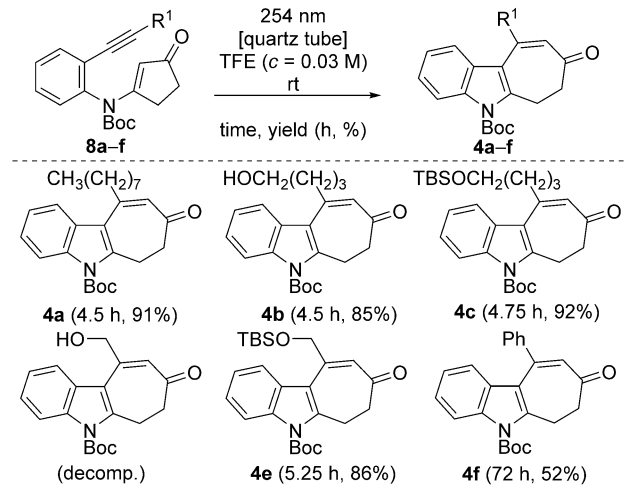
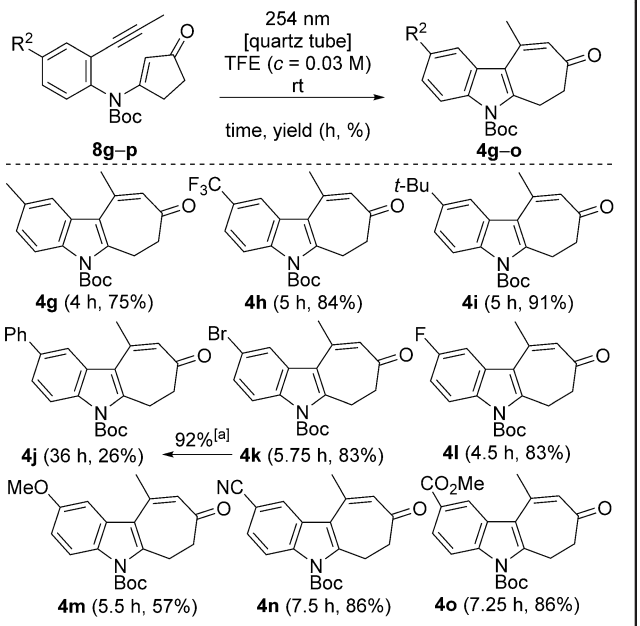
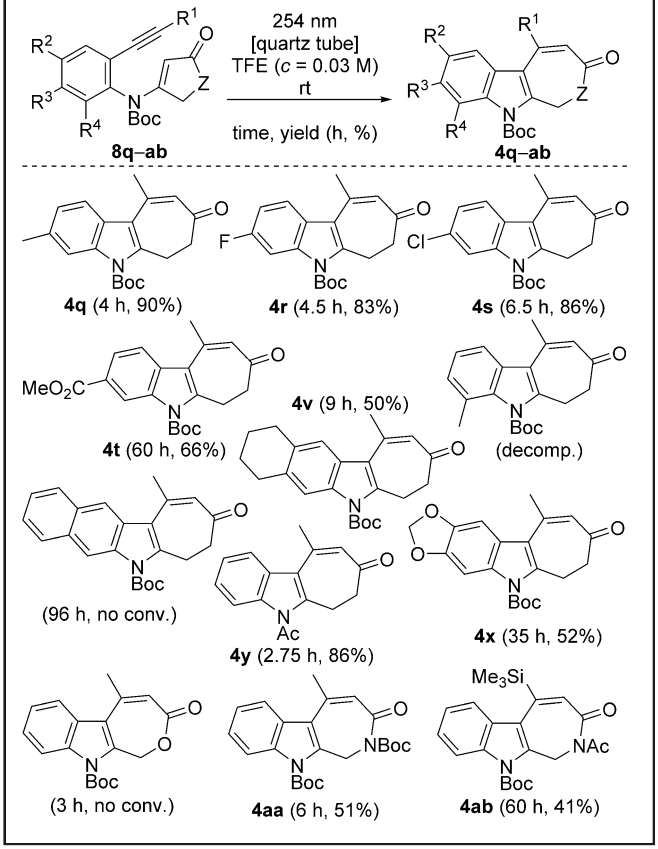


Table 2. Two-carbon ring expansion: Varying R^2.



[a] $PhB(OH)_2$ (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), PCy_3 (0.1 equiv), Cs_2CO_3 (1.5 equiv), 1,4-dioxane (297 equiv), 80 °C, 5.5 h, 92% (226 mg).

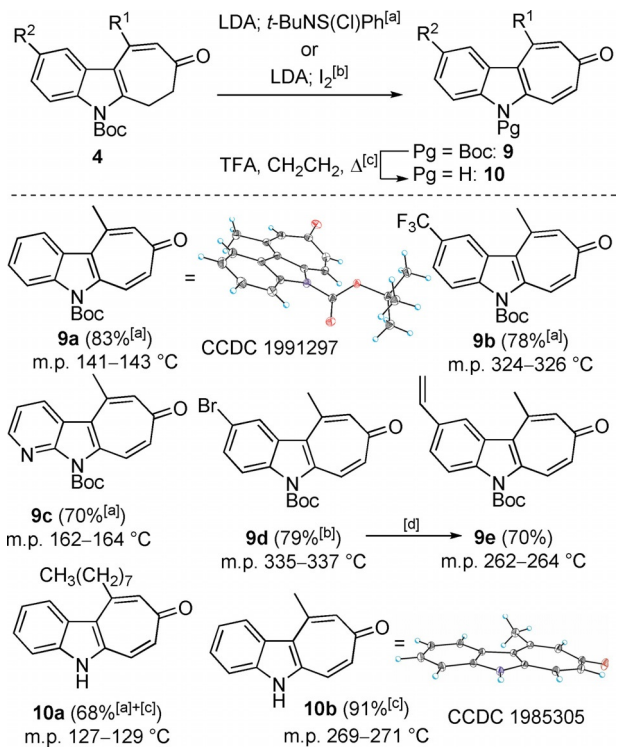
Table 3. Two-carbon ring expansion: Varying R^{1-4} and Z.



sion of *m*-aminobenzoic acid derived **8t** ($R^1 = CH_3$, $R^3 = CO_2Me$) required strikingly prolonged irradiation (60 h, **4o**: 7 h) and delivered **4t** (66%, **4o**: 86%) in moderate yield. Degradation was observed for $R^4 = CH_3$ (**8u**); in the event, we speculate that „steric hindrance" interferes with the photochemical *compress*-phase of the ring-expansion process. 2-Aminonaphthalene-based **8w** resisted irradiation (96 h) and was re-isolated (96%), whereas irradiation of the 5,6,7,8-tetrahydro-2-aminonaphthalene-based **8v** proceeded reluctantly to afford tetracyclic **4v** (50%) in moderate yield. 5-Aminobenzo[*d*][1,3]dioxole-derived **8x** successfully underwent the ring-expansion to yield tetracyclic **4x** (52%) in reasonable yield. Finally, we turned to chromophore diversification. Irradiation of *N*-acetyl derivative **8y** yielded the ring-expanded product **4y** in 86% yield after only 2.75 h of reactor running time. When irradiating tetronic acid-originated **8z** ($R^1 = CH_3$, Z = O), no conversion was detected by TLC. Tetramic acid-derived **8aa** ($R^1 = CH_3$) and **8ab** ($R^1 = Si(CH_3)_3$), however, could be converted into the desired ring-expansion products **4aa** (51%) and **4ab** (41%) with moderate success.

We are interested in utilizing indole-tropone-fused cyclohepta[*b*]indol-8-ones (indolo[2,3-*d*]tropones, **10**) as scaffold elements for the synthesis of extended *N*-heteroacenes, *N*-heterohelicenes, and as building blocks in natural product total synthesis (Table 4). Thus, we explored the dehydrogenation of selected 6,7-dihydro-cyclohepta[*b*]indol-8(5*H*)-ones **4**. The corresponding lithium enolates were treated with *N*-*tert*-butylbenzenesulfinimidoyl chloride[11] to deliver Boc-protected indolo[2,3-*d*]tropones **9**.[12,13] Purification of the thus prepared cyclohepta[*b*]indol-8-ones **9** was complicated by intractable impurities of *N*-(*tert*-butyl)-*S*-phenylthiohydroxylamine. Alternatively, the enolate of **4k** was treated with I_2 to deliver Boc protected **9d** (79%); aryl bromide **9d** is anticipated to serve as a relay compound for scaffold extension as exemplified by Suzuki cross-coupling with potassium vinyltrifluoroborate to afford **9e** (70%). Removal of the Boc protecting group delivered **10a** (68%) and **10b**[12] (91%) representing founding members of the indolo[2,3-*d*]tropone (**10**) family of compounds.[14,15,16]

Table 4. Two-carbon ring expansion: Varying R2.



[a] LDA, THF, −78 °C, then *t*BuNS(Cl)Ph, −78 °C; [b] LDA (1.5 equiv), THF, −78 °C to −50 °C, 1 h, then I_2 (1.6 equiv), −50 °C to rt, 0.5 h, 79% (207 mg); [c] TFA (28 equiv), CH_2Cl_2, 40 °C; [d] CH_2CHBF_3K (2 equiv), $Pd_2(dba)_3$ (0.1 equiv), $P(tBu)_3{\cdot}HBF_4$ (0.1 equiv), Cs_2CO_3 (3 equiv), 1,4-dioxane-H_2O (10:1), 60 °C, 30 min, 70% (108 mg).

We used experimental and computational studies to gain mechanistic insights into the ring-expansive multibond reorganization process. Experimentally, irradiation (350 nm) of **8k** in the presence of a triplet sensitizer (xanthone) triggered formation of **4k**; on the other hand, formation of **4k** was suppressed at 254 nm in the presence of a triplet quencher (2,5-dimethylhexa-2,4-diene).[17] On this basis, we assumed a [2+2] cycloaddition on the triplet surface. To gain further mechanistic insights, we performed (TD)DFT studies using the model compound **11** (Figure 3).[18,19] Our calculations on the B3LYP/def2-TZVP level of theory predict a vertical excitation of S_0-**11** to an upper S_n-state (+112.6 kcal mol^{-1}) that is followed by internal conversion (IC) to the S_1-**11** state (n,π^* character with respect to the α,β-enone segment) and intersystem crossing (ISC) to the T_1-**11** state.[20] Our computations suggest π,π^* character for T_1-**11** with spin-density being located above and below the α,β-enone segment. Subsequent low-barrier (+4.8 kcal mol^{-1}) 5-*exo*-dig cyclization to T_1-**13** via **12** is predicted to be highly exoenergetic (−21.1 kcal mol^{-1}). T_1-**13** was calculated to be almost isoenergetic to the double bond isomeric T_1-**14** (−0.5 kcal mol^{-1}); T_1-**13** is interconnected with T_1-**14** via a low-barrier transition state (+1.8 kcal mol^{-1}, not depicted). Rapid ISC of T_1-**14** to S_0-**14** is followed by an almost barrier-less (+1.1 kcal mol^{-1}) and highly exoenergetic (−42.1 kcal mol^{-1}) cyclization via **15** to the (2+2) photocycloadduct **16**. According to gas-phase DFT calculations, the π-donor–π-acceptor substituted cyclobutene segment of **16** is susceptible to a slightly endoenergetic (+2.8 kcal mol^{-1}) concerted bond reorganization via the transition-state **17** (+24.1 kcal mol^{-1}) to afford **18** featuring a *trans*-α,β-enone moiety.[21] The stereochemical result of the modeled conversion of **16** to **18** is in accordance with a bond reorganization proceeding by a conrotatory 4π-electrocyclic ring-opening. Although predicted to be highly exoenergetic, attempts to localize a pathway leading from **18** (or **16**) to the model compound **19** for the experimentally observed ring expansion-products by gas-phase computations were futile. The scale of the predicted barrier height (+24.1 kcal) for the conversion of **16** to **18** encouraged experimental studies to identify the [2+2]-cycloadduct. However, efforts to detect the elusive [2+2]-cycloadduct from **8k** by (preparative) TLC or by NMR experiments in deuterated solvents failed. The ring-opening was then re-modeled by considering explicit hydrogen-bonding interactions between two molecules of 2,2,2-trifluor-

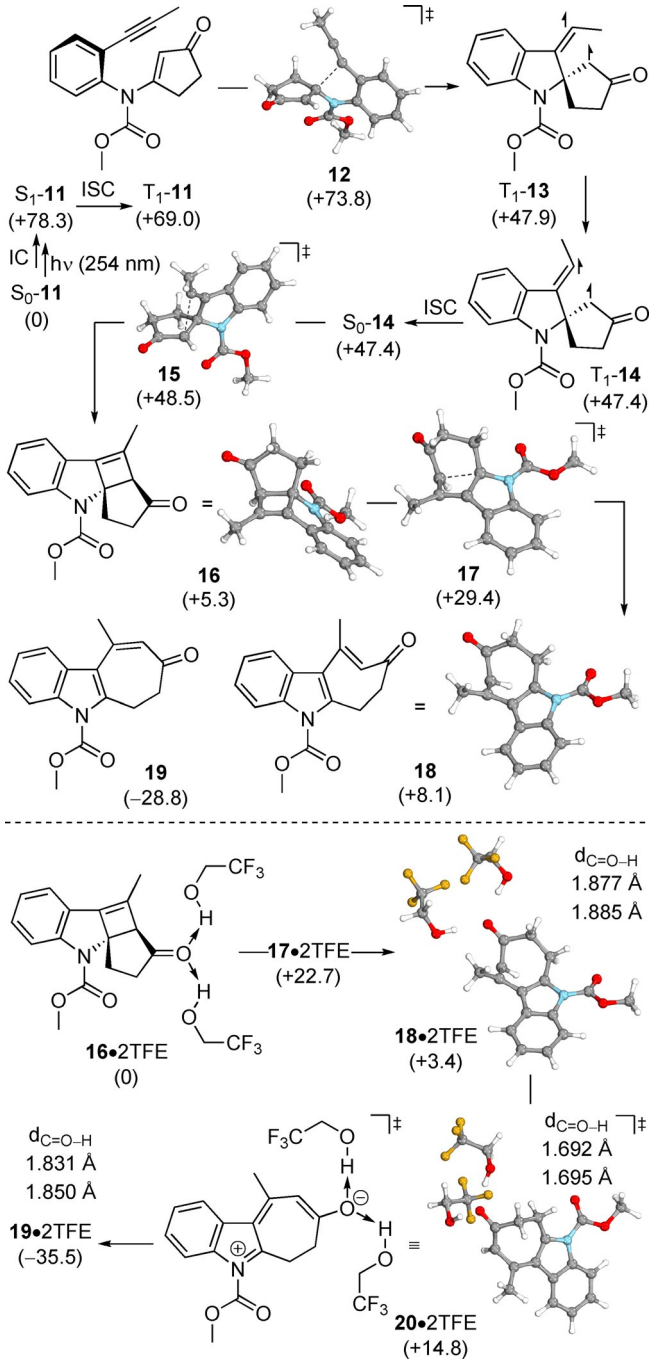


Figure 3. (TD)DTF (u)B3LYP/def2-TZVP calculated (relative) electronic plus zero-point energies (ΔE) at 298.15 K in kcal mol^{-1}.

oethanol (TFE) and the carbonyl oxygen atom of **16** (Figure 3). Our DFT calculations predict a slightly lower barrier for the weakly endoenergetic electrocyclic ring-opening of **16**·2TFE via **17**·2TFE (+22.7 kcal mol^{-1}, not depicted; corresponds to a calculated $t_{1/2}$ = 81 min) to **18**·2TFE (+3.4 kcal mol^{-1}). Notably, however, consideration of explicit hydrogen bonding interactions opens a low-barrier (+11.2 kcal mol^{-1}) pathway for the double-bond isomerization of **18**·2TFE to **19**·2TFE (−35.5 kcal mol^{-1}, not depicted) via **20**·2TFE. The transition-state structure **20**·2TFE may be best explained as a tightly hydrogen-bonded non-π-resonating α,β-eniminium-enolate zwitterion that we could not locate computationally without considering the transition-state stabilizing interaction with TFE. Experimentally, attempts to perform the two-carbon ring-expansion of **8k** in CH_3CN or CH_3OH led to considerably lower isolated yields of **4k** (CH_3CN: 61%; CH_3OH: 33%). In both cases **4k** was contaminated with unidentified inseparable impurities. To further study the apparent solvent effect, control experiments were run in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). Much to our initial surprise, the resulting isolated yields were considerably lower (HFIP: 66%, TFE: 83%) **4k** but free of detectable impurities. We later realized that the comparatively lower yields in HFIP can be attributed to the cleavage of the Boc protecting group in HFIP [22] which slowly proceeds even at ambient temperature without irradiation.

In summary, we reveal a conceptually novel approach to the cyclohepta[*b*]indole scaffold. Irradiation (254 nm) of modularly assembled vinylogous amides from 2-alkynyl anilines in 2,2,2-trifluoroethanol at ambient temperature triggered an intramolecular one-pot annulative two-carbon ring expansion to deliver 6,7-dihydro-cyclohepta[*b*]indol-8(5*H*)-ones. The process merges exited-state [2+2]-cycloaddition with ground-state 4π-electrocyclic ring-opening. Computational chemistry suggests that solvent cooperativity is fundamental to the success of the overall multibond reorganization process. We also report the post-irradiative synthesis and characterization of founding members of the indolo[2,3-*d*]tropone family of compounds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cascade reactions · cyclohepta[*b*]indole · indole[2,3-*d*]tropone · photochemistry · ring expansion

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