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Synthesis of Indanones via Solid-Supported [2+2+2] Cyclotrimerization

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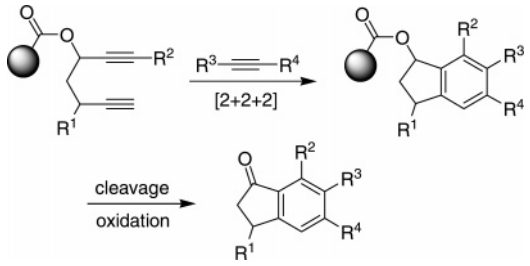

A new facile approach toward natural and unnatural indanones has been developed, featuring a solid-supported [2+2+2] cyclotrimerization as the key step. This strategy has been applied to the chemo- and regioselective assembly of indanone arrays and to the total synthesis of a recently isolated indanone marine natural product.

Recently we initiated a program in developing solid-supported [2+2+2] cyclotrimerization reactions and applying these reactions to the synthesis of functional molecules.[1,2] [2+2+2] cyclotrimerization reactions are versatile tools in the assembly of carbo- and heterocyclic structures,[3] and they have been previously employed as key steps in total syntheses.[4−6] However, their application is often hampered by regio- and chemoselectivity problems leading to complex product mixtures. This is especially pronounced in cases where triple bonds with greatly different reactivity (e.g., due to different substitution patterns) are employed.[3] Conducting [2+2+2] cyclotrimerization reactions on a solid support can solve these problems, and we recently accomplished the first highly selective formation of pyridines via this strategy.[1] Here we are reporting a new synthetic route to natural and unnatural indanones via regio- and chemoselective solid-supported [2+2+2] cyclotrimerization reactions. Previous indanone syntheses via cycloadditions either involved completely intramolecular cyclotrimerization reactions,[4,7] cyclotrimerization of enones,[8] or cyclotrimerization reactions with low regioselectivity.[9]

The indanone core structure is widely disseminated among pharmacologically active substances with a wide range of biological activities, hence efficient and selective approaches to their synthesis are in demand.[10] Additionally, hundreds of indanone natural products are known,[11,12] most importantly the pterosins (Figure 1), including pterosin P (**1**), mukagolactone (**2**), and monachosorin A (**3**).[13]

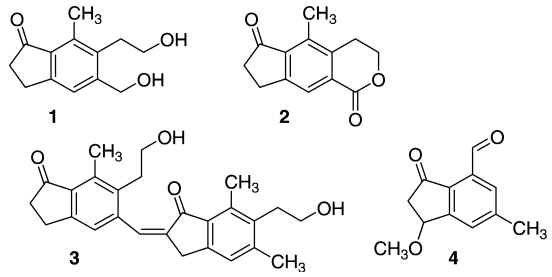

FIGURE 1. Selected indanone natural products **1**−**4**.

These molecules, and related structures, display a variety of biological activities including smooth muscle relaxant activity,[14] inhibition of cyclooxygenase,[15] and mast cell stabilization.[16] Recently, the indanone natural product **4** has been isolated from a marine cyanobacterium.[17] This compound shows promising biological activity as a regulator of tumor angiogenesis by inhibiting human vascular endothelial growth factor production. However, low in vivo activity observed after the initial screening requires additional structural modifications for further improvement,[17] but no total synthesis of **4** has been reported to date.

Our synthetic route to indanones commences with the cyclotrimerization precursor **5**, which was rapidly assembled

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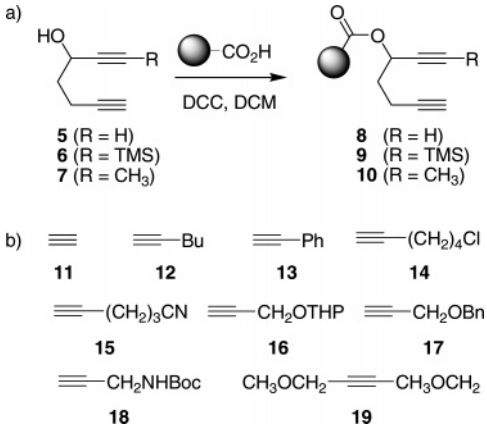
SCHEME 1. (a) Synthesis of Immobilized Cyclotrimerization Precursors 5−7 and (b) Alkyne Reaction Partners 11−19

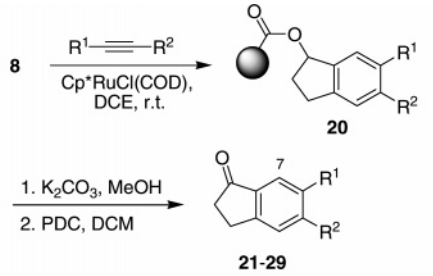


in only 2 steps.[18] On the basis of our previous results with [2+2+2] cyclotrimerization reactions, conducting the reaction via spatial separation of diyne starting materials on a solid support alleviates chemoselectivity issues prevalent in solution such as the di- and trimerization of starting materials.[1,2,19,20] Performing these reactions on a solid support, especially with a low loading of 0.2 mmol g^{-1}, prevents these side reactions despite the flexibility of the employed TentaGel resin (NovaSyn TG, NovaBiochem, loading 0.25 mmol/g). This affords significantly higher yields and products of higher purity (especially in the case of less reactive internal monoalkynes). A high level of synthetic flexibility was achieved by employing an immobilization strategy in which the position of linkage to the solid phase is not visible in the final product.[21]

Due to the acid-sensitive nature of the benzylic C−O bond in the indanol cyclotrimerization products, the alcohol **5** was immobilized via a carboxy linker that can be cleaved under mild basic conditions. Initial experiments with an acid-cleavable Wang or trityl linker did not deliver any product. The immobilized **8** was assembled by reacting the resin with **5** (5 equiv) in the presence of DCC in DCM, and a loading of 0.2 mmol g^{-1} was obtained (as determined by GC/MS analysis). The excess of diyne **5** could be fully recovered.

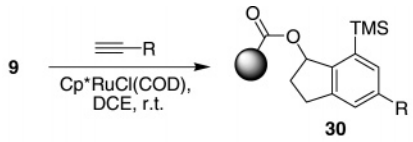
The first cyclotrimerization attempts with **8** by using the classical Wilkinson's catalyst ($RhCl(Ph_3P)_3$)[19,22] led to inconclusive results and cleavage of the diyne from the resin, although propargyl acetates have previously been employed in Rh-catalyzed cyclotrimerizations.[6,19,23] The [2+2+2] cyclotrimerization proceeded smoothly at room temperature when Cp*Ru(COD)Cl was used as a catalyst.[20] A set of nine alkynes (**11**−**19**, Scheme 1) was investigated, revealing that the reaction was compatible with a variety of functionalities, including alkyl chains (in **12**), aromatic rings (in **13** and **17**), alkoxy groups (in **16**, **17**, and **19**), carbamates (in **18**), halides (in **14**), and cyano groups (in **15**). The cyclotrimerized products were released from the resin by treatment with K_2CO_3 in MeOH/THF. A subsequent solvent change to CH_2Cl_2 followed by oxidation with PDC delivered the indanones **21**−**29** in good yields (58−78% over three steps) and with excellent purity (>90% by ^1H NMR and GC/MS analysis). Alternative oxidizing agents (e.g., MnO_2 and Dess−Martin's periodinane) delivered indanones in slightly lower yields.

SCHEME 2. Solid-Supported Formation of Indanones 21−29



Compound	R^1	R^2	Yield	a/b
21	H	H	78%	
22a	Bu	H	65%	1:2
22b	H	Bu		
23a	Ph	H	62%	2:3
23b	H	Ph		
24a	$(CH_2)_4Cl$	H	72%	2:3
24b	H	$(CH_2)_4Cl$		
25a	$(CH_2)_3CN$	H	61%	2:3
25b	H	$(CH_2)_3CN$		
26a	CH_2OBn	H	66%	1:2
26b	H	CH_2OBn		
27a	CH_2OTHP	H	65%	1:2
27b	H	CH_2OTHP		
28a	CH_2NBoc	H	70%	1:2
28b	H	CH_2NBoc		
29	CH_2OCH_3	CH_2OCH_3	58%	

SCHEME 3. Regioselective Solid-Supported [2+2+2] Cyclotrimerization toward Indanones



Cmpd	Yield	R
22b	71%	Bu
23b	66%	Ph
24b	57%	$(CH_2)_4Cl$
25b	69%	$(CH_2)_3CN$
26b	71%	CH_2OBn

Since the reaction mechanism does not allow differentiation between the two triple bonds in the precursor **8**, mixtures of two regioisomers are observed. The regioisomeric ratio, as determined by ^1H NMR, ranges from 1:2 to 2:3, with a minimal preference for the formation of the regioisomers **22b**−**28b**. The regioisomeric ratio shown for **22**−**28** was determined based on the integration of the signal for the aromatic proton at C-7, which occurs farthest downfield in the NMR spectrum. In the case of regioisomers **22a**−**28a** the signal for the proton at C-7 is a singlet, while in the opposite regioisomers **22b**−**28b** this signal occurs as a doublet. This regioisomer assignment was later confirmed by the regioselective preparation of **22b**−**26b** (see Scheme 3).

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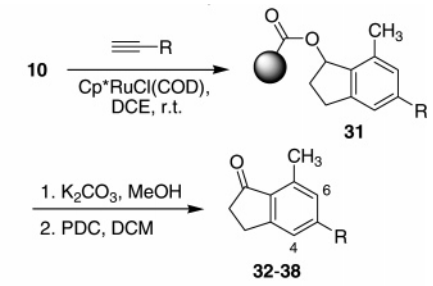
To demonstrate the enhancing effect of the solid support, a solution-phase three-step transformation of *O*-acetylated **5** to **22** under conditions resembling the solid-phase reaction (20 mM substrate, 10 equiv of 1-hexyne) was conducted. This led to a diminished overall yield of 28% (the solution-phase cyclotrimerization step alone only showed a 37% yield, 1:2 regioselectivity) for **22**. This lower yield is a result of competing side reactions in the [2+2+2] cyclotrimerization step (as discussed earlier), which are not observed on the solid support. Previously, the di- and trimerization of diyne starting materials has been addressed in a less general fashion through the usage of internal diynes or the application of high-dilution conditions in conjunction with a slow diyne addition over an extended period of time.[3]

Even though the formation of two regioisomers increases the structural diversity in generated indanone arrays, a selective cyclotrimerization leading to only one product is highly desirable. To impose regioselectivity on the solid-supported cyclotrimerization, the precursor **9** was synthesized bearing a removable regiodirecting group (TMS).[4] Due to the steric bulk of the TMS group, the *meta* isomer **30** is expected to be the major product (Scheme 3). Cyclotrimerization reactions were carried out with terminal alkynes under standard conditions, followed by cleavage and oxidation.[20] Investigations into removal of the TMS group were conducted on both the reduced and oxidized indanone. Traditional conditions (TFA, HBr, TBAF, and NH_4F) all yielded little to no desilylation at room temperature or at elevated temperature.[24] The TMS group was ultimately removed by treatment with TBAF in 4:1 THF/DMF under microwave irradiation, delivering the indanones **22b**−**26b** in good yields (57−74% over the complete 4-step procedure) and as single regioisomers.

The regioisomer shown for **22b**−**26b** was assigned based on the ^{1}H NMR spectrum, which displays a doublet for the downfield shifted proton H-7 due to its coupling to H-6. The ^{1}H NMR spectra of the products correspond to a single regioisomer when compared to the mixtures previously obtained (see Scheme 2). On the basis of the integration of the NMR signal for H-5 the regioisomeric ratio was determined to >95:5. Overall, the [2+2+2] cyclotrimerization reactions of the sterically more hindered **9** lead to comparable product yields to the non-silylated substrate **8**, while delivering pure regioisomers.

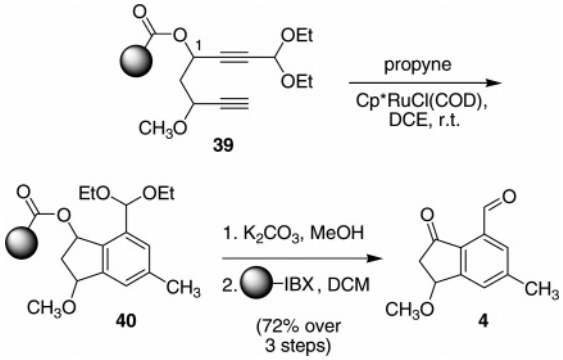
These studies demonstrate the applicability of solid-supported cyclotrimerizations to the chemo- and regioselective formation of natural and unnatural indanones. Since several indanone natural products display a methyl group in the 7-position,[11] the cyclotrimerization precursor **10** was assembled (following a previously employed protocol[18]). Although a highly regioselective [2+2+2] cyclotrimerization as in the case of **9** was expected, the regioselectivity inducing effect of a sterically smaller methyl group (compared to a TMS group) needed to be investigated. The reaction of **10** with terminal alkynes via the standard cyclotrimerization protocol smoothly led to the formation of **31** (Scheme 4), followed by the cleavage−oxidation sequence yielding the methyl indanones **32**−**38** as the only regioisomers. Yields for the three-step process ranged from 63% to 74% and purities were observed to be >90%. The regioisomer shown for **33**−**38** was assigned based on singlets in the ^{1}H NMR spectrum for the aromatic protons at both C-6 and C-4. In the case of the opposite regioisomer, doublets for those protons would be expected. On the basis of these assignments in the NMR spectrum the regioisomeric ratio was determined to >95:5.

SCHEME 4. Regioselective Solid-Supported [2+2+2] Cyclotrimerization toward Methyl-Substituted Indanones



Compound	R	Yield
32	H	74%
33	Bu	67%
34	Ph	66%
35	$(CH_2)_4Cl$	63%
36	$(CH_2)_3CN$	71%
37	CH_2OTHP	63%
38	CH_2NHBoc	67%

SCHEME 5. Solid-Supported Synthesis of the Indanone Natural Product 4



These results set the stage for the synthesis of indanone natural products via solid-supported [2+2+2] cyclotrimerizations. We selected the marine natural product **4**, which was recently isolated from the filamentous marine cyanobacterium *Lyngbya majuscula*,[17] as a target molecule since no total synthesis has been reported to date. Moreover, it exhibits promising antiangiogenesis activity,[17] which could potentially be improved through the availability of a facile synthetic approach to analogues. The immobilized cyclotrimerization precursor **39** was assembled in 7 steps from known material (see the Supporting Information). Again, a carboxy linkage to the polymeric support was chosen due to the acid lability of the indanol (as discussed above). Since the natural product was reported to be nearly racemic no attempt to generate enantiomerically pure **39** was undertaken. The precursor **39** was cyclotrimerized with propyne to furnish immobilized **40** under the conditions established in previous experiments. After treatment of **40** with K_2CO_3 in THF/MeOH the resulting indanol was oxidized with solid-supported IBX (2-iodoxybenzoic acid polystyrene, Novagen), conveniently leading to an unexpected acetal cleavage by the solid-supported oxidizing agent. The natural product **4** was obtained in excellent yield (72% over

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three steps) and as the only regioisomer. All spectroscopic data are in agreement with the literature.[17]

In contrast, solution-phase [2+2+2] cyclotrimerization reactions toward **4** were much less successful. A trityl protected precursor of **39** (see the Supporting Information) failed to undergo cyclotrimerization, most likely due to strong sterical interactions in the aromatic product between the trityl group on O-1 and the diethylacetal. The solution-phase [2+2+2] cyclotrimerization of an O-1 acetylated precursor (not shown), resembling the carboxy linker in **39**, provided the cyclotrimerization product in only 56% yield. This yield is considerably lower than the 72% yield in the case of the solid-phase reaction shown in Scheme 5, which also includes the subsequent deprotection and oxidation. Thus, the solid-phase cyclotrimerization approach enables the facile synthesis of analogues of **4** to further improve its antiangiogenesis activity.

In summary, an efficient and facile approach to natural and unnatural indanones via a solid-supported [2+2+2] cyclotrimerization has been accomplished. An immobilization strategy was realized that does not show any remains of the linkage site to the solid support in the final product. Chemo- and regioselectivity issues typically observed in cyclotrimerization reactions have been resolved, and arrays of differently substituted indanones have been constructed. The applicability of the developed approach to total synthesis has been demonstrated through the assembly of a marine natural product. The biological activities of the synthesized compounds, especially of **4** and analogues thereof, will be investigated in due course.

Experimental Section

General Diyne Immobilization Procedure. Carboxylic acid derivatized resin (1.0 g, 1.2 mmol) was allowed to swell for 15 min in DCM (6 mL). The diyne (6 mmol) was added, followed by DMAP (29 mg, 0.24 mmol) and dicyclohexylcarbodiimide (0.93 mL, 6 mmol), and the reaction was shaken at room temperature for 12 h. The resin was transferred to a syringe filter and washed with alternating rinses of DCM and MeOH (4 × 5 mL). The resin was dried under vacuum and an aliquot of 15 mg was cleaved (25 mg of K_2CO_3, 500 μL 4:1 THF/MeOH, 12 h). The loading was determined via GC/MS analysis by generating a standard curve of the diyne starting material within the range of expected loading (100, 50, and 25 mM).

General Cyclotrimerization Procedure. Diyne derivatized resin (50 mg, 0.05 mmol) was placed into a flame-dried vial and was suspended in dichloroethane (2 mL) under a nitrogen atmosphere. The soluble alkyne (0.50 mmol) was added and the solution was degassed with 3 freeze−pump−thaw cycles. The Cp*Ru(COD)Cl catalyst (2 mg, 0.01 mmol) was added and the reaction was shaken at room temperature for 24 h. The resin was then transferred to a syringe filter, washed with alternating rinses of DCM and MeOH (4 × 3 mL), and subsequently dried under vacuum.

General Cleavage and Oxidation Procedure. Dried resin carrying the cyclotrimerized product was transferred to a vial, THF and MeOH (4:1, 500 μL) were added followed by K_2CO_3 (20 mg, 0.14 mmol), and the suspension was shaken for 16 h at room temperature. The filtrate was removed, concentrated, and dissolved in DCM (1 mL). PCC (15 mg, 0.07 mmol) or PDC (26 mg, 0.07 mmol) was added and the solution was stirred overnight at room temperature. The reaction mixture was filtered through a silica plug followed by a rinse with DCM (2 mL), and concentrated to yield pure indanone products. All yields were determined by measuring the mass balance of pure indanones and correlating the amount of material to the loading of the resin.

General Desilylation Procedure. Oxidized TMS−indanones were dissolved in THF (400 μL), transferred to a microwave vial, and treated with DMF (100 μL) followed by 1.0 M TBAF in THF (50 μL, 0.05 mmol), and the reaction was placed in a CEM Discover Microwave Synthesizer for 2 min (300 W, ∼200 °C). The reaction was then passed through a silica plug that was subsequently rinsed with hexanes (2 mL), and the filtrate was concentrated to yield pure desilylated indanone products. Overall indanone yields ranged from 57% to 78% and products were obtained in quantities of 2.6−7.2 mg.

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Supporting Information Available: Analytical data of indanones **21**−**38**, synthesis of **4** and **39**, and ^{1}H NMR spectra of compounds **4**, **21**−**29**, and **32**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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