# $InCl_3$-Mediated Cascade Reactions for the Construction of Highly Functionalized 1-Oxadecalins

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**Abstract:** A one-pot, two-component $InCl_3$-mediated cascade reaction has been developed. Starting from readily available β-keto ester and alkynal substrates, this cascade reaction provided highly functionalized 1-oxadecalins in good yields and excellent diastereoselectivities.

**Key words:** 1-oxadecalin, indium, cascade cyclizations, Prins, Conia–ene reactions

1-Oxadecalins are bicyclic ring systems containing a tetrahydropyranyl unit fused to a cyclohexane ring. Since this structural motif can be found in many natural products with interesting biological activities (Figure 1),[1] a variety of methods have been developed for the construction of this ring system.[2] Among the most popular methods are Diels–Alder-type cycloadditions,[3] polyene cyclizations,[4] and tetrahydropyran formations via various reactions, such as conjugate additions,[5] epoxide-opening reactions,[6] Prins-type reactions,[7] and radical cyclizations.[8] We are particular interested in developing new cascade reactions for the construction of various ring systems because they often enable the generation of the core ring structure with multiple stereogenic centers in a single synthetic operation.[9] Herein we report a highly diastereoselective $InCl_3$-mediated cascade reaction for construction of highly functionalized 1-oxadecalins via a one-pot, two-component method.

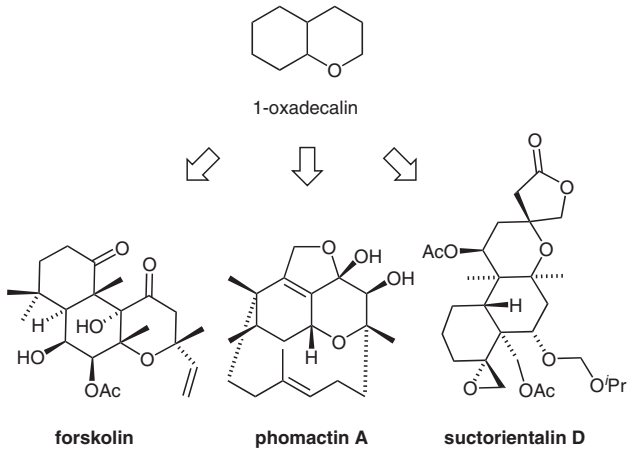


**Figure 1** Examples of natural products bearing 1-oxadecalin

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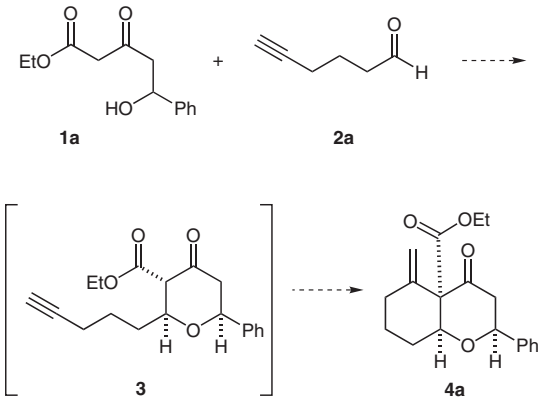
Our approach involves a Lewis acid mediated Maitland–Japp-type[10] reaction between β-keto ester **1a**[11] and hex-5-ynal[12] (**2a**) to give tetrahydropyran **3**. Under the appropriate conditions, the Lewis acid should be able to facilitate the enolization of **3** and induce the subsequent Conia–ene reaction to establish the oxadecalin ring system of **4a** in a one-pot process (Scheme 1). Since Ti(IV) has been reported to be effective for both Maitland–Japp-type[10b,c] and Conia–ene reactions,[13] its utility in the cascade reaction was first investigated.




**Scheme 1**

As shown in Table 1,[14] $TiCl_4$ in THF gave a moderate yield of tetrahydropyran **3**, which was found to be a single diastereomer containing 10% of the enol tautomer in $CDCl_3$.[15] However, switching the solvent to $CH_2Cl_2$ led to decomposition of the substrates. Clarke's modified Maitland–Japp conditions[10a] also afforded **3** in good yields (entry 3). Unfortunately, attempts to induce the subsequent Conia–ene reaction by increasing the reaction temperature failed and resulted in decomposition of **3**. A variety of effective Lewis acids for Conia–ene reactions were also examined. Mercury(II) chloride[16] gave only trace amount of **3** and no vinylmercurial intermediate was observed. Employing Yang's conditions[17] resulted in only a trace amount of tetrahydropyran formation (entry 6). The yield of **3** was improved by switching the solvent to $CH_2Cl_2$ with $Yb(OTf)_3$ alone. However, the combination of $Yb(OTf)_3$/$Ni(acac)_2$ in $CH_2Cl_2$ gave primarily tetrahydropyran **3**, which decomposed slowly under the reaction conditions (entry 8). No reaction was observed using Toste's conditions,[18] and the alkynal substrate decomposed generally by increasing the Au(I) catalysts from 1

to 10 mol% (entry 9). Ley's conditions[19] were also investigated. Upon treatment with $SnCl_4$, both starting materials were consumed after 20 hours in refluxing $CH_2Cl_2$ and 20% of the expected oxadecalin product **4a** was obtained. Zinc iodide also afforded **4a** in 15% yield along with 55% of **3** (entry 11). However, extended heating of the mixture led to decomposition of both **3** and **4a**. With these encouraging results, Nakamura's conditions[20] were studied. Catalytic amount of $In(OTf)_3$ in refluxing $CH_2Cl_2$ afforded only tetrahydropyran **3** as the product (entry 12), and only 11% of **4a** was obtained by increasing the amount of $In(OTf)_3$ to 1 equivalent (entry 13). By switching the solvent to toluene, both substrates were consumed after 20 hours in 100 °C with 10 mol% of $In(OTf)_3$ and afforded 37% of **4a**. Finally, we found that a stoichiometric amount of $InCl_3$ in refluxing $CH_2Cl_2$ afforded a 73% yield of **4a** in 7 hours (entry 15). Oxadecalin **4a** was found to be a single diastereomer bearing a *cis* ring junction with a chair–chair conformation (Figure 2).[20]

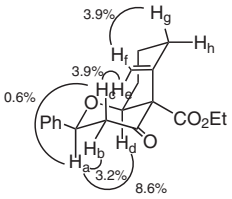



**Figure 2** The NOE (%) of oxadecalin **4a**

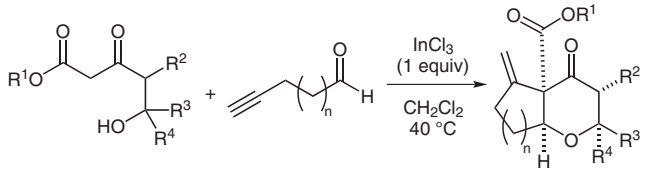
**Table 1** Synthesis of 1-Oxadecalins via Cascade Reactions[a]

| Entry | Lewis acid | Solvent | Temp | Time (h) | Yield (%)[b] | |
|---|---|---|---|---|---|---|
| | | | | | **3** | **4a** |
| 1 | $TiCl_4$ | THF | 0 °C to r.t. | 18 | 38 | – |
| 2 | $TiCl_4$ | $CH_2Cl_2$ | 0 °C to r.t. | 36 | – | – |
| 3 | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | 0 °C | 2 | 63 | – |
| 4 | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | 0 °C to 40 °C | 36 | 14 | – |
| 5 | $HgCl_2$ | $CH_2Cl_2$ | reflux | 36 | trace | – |
| 6 | $Yb(OTf)_3/Ni(acac)_2$[c] | 1,4-Dioxane | r.t. to 80 °C | 36 | trace | – |
| 7 | $Yb(OTf)_3$ | $CH_2Cl_2$ | 40 °C | 36 | 53 | – |
| 8 | $Yb(OTf)_3/Ni(acac)_2$ | $CH_2Cl_2$ | 40 °C | 48 | 28 | – |
| 9 | $Ph_3PAuCl/AgOTf$[d] | $CH_2Cl_2$ | r.t. to 40 °C | 36 | – | – |
| 10 | $SnCl_4$ | $CH_2Cl_2$ | 40 °C | 20 | – | 20 |
| 11 | $ZnI_2$ | $CH_2Cl_2$ | 40 °C | 36 | 55 | 15 |
| 12 | $In(OTf)_3$[e] | $CH_2Cl_2$ | 40 °C | 24 | 46 | – |
| 13 | $In(OTf)_3$[f] | $CH_2Cl_2$ | 40 °C | 24 | 39 | 11 |
| 14 | $In(OTf)_3$[e] | Toluene | 100 °C | 20 | – | 37 |
| 15 | $InCl_3$ | $CH_2Cl_2$ | 40 °C | 7 | – | 73 |
| 16 | $InCl_3$ | $CHCl_3$ | 40 °C | 7 | – | 71 |
| 17 | $InCl_3$ | THF | r.t. to 40 °C | 36 | – | – |
| 18 | $InCl_3$ | THF–$H_2O$ (4:1) | r.t. to 40 °C | 12 | – | – |
| 19 | $InCl_3$ | Toluene | 40 °C | 36 | 35 | 20 |
| 20 | $InCl_3$ | Toluene | 70 °C | 36 | – | 56 |
| 21 | $InCl_3$ | MeCN | 40 °C | 36 | 13 | 54 |
| 22 | $InCl_3$ | MeCN | 70 °C | 30 | – | 69 |

[a] The general procedures were followed.
[b] Isolated yields after flash column chromatography.
[c] The amount of 10–100 mol% of $Yb(OTf)_3/Ni(acac)_2$ were used.
[d] The amount of 1–10 mol% of $Ph_3PAuCl/AgOTf$ were used.
[e] The amount of 10 mol% of $In(OTf)_3$ was used.
[f] 1 Equiv of $In(OTf)_3$ was used.

To optimize the conditions of the cascade reaction, a solvent effect survey was conducted. The cascade reaction went smoothly in $CHCl_3$ and gave good yields of **4a**. However, using THF and THF–$H_2O$ mixture as the solvent led to decomposition of the substrates (entries 17 and 18). Toluene and MeCN also afforded the oxadecalin product in moderate to good yields but these solvents required a higher reaction temperature and longer reaction time (entries 20 and 22). With the solvent optimized, the effects of the $InCl_3$ loading were investigated. The cascade reaction was found to proceed with 0.1–0.5 equivalents of $InCl_3$. However, slow and incomplete reaction was observed after 1 day in refluxing $CH_2Cl_2$ (data not shown). Attempts to remove the water generated in situ by adding 3 Å molecular sieves in the reaction mixture failed to improve the efficiency of the reaction.

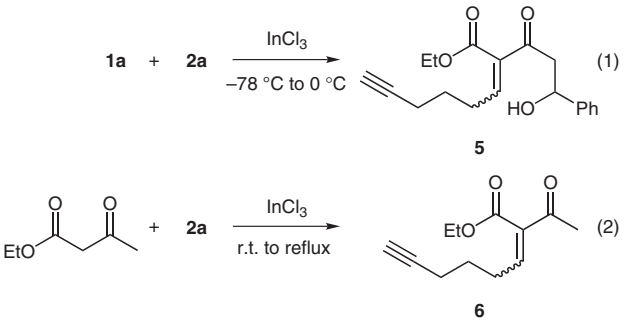
**Table 2** $InCl_3$-Mediated Cascade Reactions[a]




| Entry | 1 | 2 | 4 | n | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%)[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **a** | **a** | **a** | 2 | Et | H | Ph | H | 73[c] |
| 2 | **b** | **a** | **b** | 2 | Et | H | *n*-Hept | H | 72[c] |
| 3 | **c** | **a** | **c** | 2 | Et | H | *i*-Pr | H | 81[c] |
| 4 | **d** | **a** | **d** | 2 | Et | H | *c*-Hex | H | 72[c] |
| 5 | **e** | **a** | **e** | 2 | Et | H | Me | Me | 52[c] |
| 6 | **f** | **a** | **f** | 2 | Me | Me | Ph | H | 71[d] |
| 7 | **a** | **b** | **g** | 1 | Et | H | Ph | H | 70[c] |

[a] The general procedures were followed.
[b] Isolated yield after flash column chromatography.
[c] The product was found to be a single diastereomer and the relative stereochemistry was determined by NOE.
[d] A 3:1 mixture of diastereomers was obtained and the relative stereochemistry was determined by NOE.

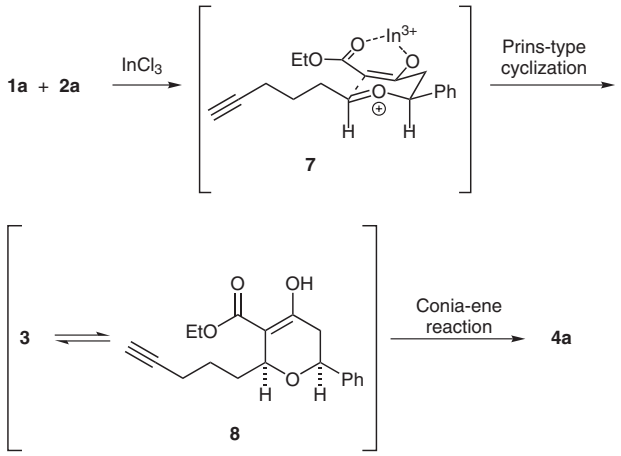
The scope of the cascade reaction was studied using a number of different β-keto esters **1b–f**, which were prepared via the dianion addition of ethyl acetoacetate or methyl propionylacetate to the appropriate aldehyde or ketone.[10a,11] As shown in Table 2,[21] $InCl_3$-mediated cascade reactions of β-keto esters **1b–d** with hex-5-ynal went smoothly in refluxing $CH_2Cl_2$ and gave oxadecalin **4b–d** in good yields. These results indicated that changing the phenyl group to alkyl groups with different steric properties did not seem to affect the efficiency of the reactions. The cascade reaction of the sterically demanding substrate **1e** can also be achieved in 36 hours and gave a 52% yield of the product (entry 5). Racemic β-keto ester **1f** gave good yields of **4f**, which was found to be a 3:1 mixture of diastereomers. The two diastereomers were separable by silica gel flash column chromatography, and the major diastereomer was identified to be the oxadecalin product bearing the equatorial methyl group α to the ketone, which was presumably the thermodynamic product. The minor diastereomer could be equilibrated slowly to the major one by resubmission it back to the reaction conditions, and the *cis* ring junction remained intact under extended heating in $CH_2Cl_2$. In addition, a 5,6-oxabicyclic ring system could be obtained using pent-4-ynal[22] (**2b**) as the alkynal substrate (entry 7).




**Scheme 2**

Inspired by Clarke's mechanistic study on the modified Maitland–Japp reaction,[10a] it was reasonable to assume a Knoevenagel condensation between the β-keto ester and hex-5-ynal, followed by an intramolecular oxa-Michael addition to form tetrahydropyran **3**. The high diastereoselectivity for the formation of **3** could be rationalized by a repeated Michael–retro-Michael reaction of **5** before the second ring formation via the Conia–ene reaction. However, several attempts to isolate the Knoevenagel condensation product **5** at low reaction temperatures failed (Scheme 2). Moreover, we found that $InCl_3$ failed to induce Knoevenagel condensation between ethyl acetoacetate and hex-5-ynal in refluxing $CH_2Cl_2$. This result suggested that β-keto ester **1a** and hex-5-ynal (**2a**) may not be able to undergo Knoevenagel condensation under the cascade reaction condition. Thus, we proposed a Prins-type cyclization of an oxocarbenium ion **7** for the tetrahydropyran formation (Scheme 3).[7] The high diastereoselectivity could be rationalized by the six-membered chair-like transition state of **7**. The subsequent Conia–ene reaction of **3** presumably proceeded via the enol tautomer **8**, which could lead to the *cis*-oxadecalin ring junction selectively.

In summary, we have developed a one-pot, two-component $InCl_3$-mediated cascade reaction for construction of highly functionalized 1-oxadecalins. The cascade reaction rapidly established the 1-oxadecalin ring system from readily available β-keto ester and alkynal substrates under mild conditions with high efficiency and selectivity. We are currently exploring the utility of this method for synthesis of 1-oxadecalin-containing natural products.




**Scheme 3**

## Acknowledgment

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(14) **General Procedures**
To a stirred solution of a β-keto ester (1.5 equiv) and an alkynal (1 equiv) in the appropriate solvent (alkynal concentration = 0.1 mol/L) at 0 °C or r.t. was added a Lewis acid (1 equiv or the amount indicated). The resulting mixture was stirred at the indicated reaction temperature and the reaction was monitored by TLC analysis. After the substrates and intermediates were consumed, the mixture was cooled to r.t., treated with sat. aq $NaHCO_3$, and extracted with EtOAc (3×). The combined extracts were washed with brine and $H_2O$, dried over anhyd $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexane–EtOAc = 100:1 to 70:1).

(15) Tetrahydropyran **3**: colorless oil. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 12.21 (s, 0.1 H), 7.30–7.42 (m, 5 H), 4.74 (dd, *J* = 3, 12 Hz, 0.9 H), 4.63–4.68 (m, 0.1 H), 4.57 (dd, *J* = 4, 10 Hz, 0.1 H), 4.22–4.34 (m, 2 H), 4.07–4.15 (m, 2 H), 3.38 (d, *J* = 11 Hz, 1 H), 2.75 (dd, *J* = 3, 14 Hz, 1 H), 2.57 (dd, *J* = 12, 14 Hz, 1 H), 2.22–2.26 (m, 2 H), 1.95 (t, *J* = 3 Hz, 1 H), 1.68–1.90 (m, 4 H), 1.32 (t, *J* = 7 Hz, 3 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 201.7, 168.0, 140.2, 128.7, 128.2, 125.5, 83.9, 78.4, 78.3, 68.7, 62.9, 61.3, 48.8, 33.9, 24.3, 18.2, 14.2. HRMS (+ESI): *m/z* calcd for $C_{19}H_{22}O_4Na^+$ [M + $Na^+$]: 337.1416; found: 337.1433. The NOE (%)of **3** are consistent with the boat conformation of a similar compound (E = $CO_2Me$, R = *i*-Pr) that reported in the literature (Figure 3).[10a]

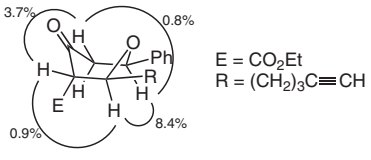


**Figure 3**

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(20) Oxadecalin **4a**: colorless oil (73%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.38 (m, 5 H, Ph), 5.22 (d, *J* = 2 Hz, 1 H, $H_f$), 4.82 (dd, *J* = 3, 12 Hz, 1 H, $H_a$), 4.57 (d, *J* = 2 Hz, 1 H, $H_e$), 4.55 (t, *J* = 3 Hz, 1 H, $H_d$), 4.25–4.32 (m, 2 H, ethyl ester), 2.92 (dd, *J* = 12, 15 Hz, 1 H, $H_c$), 2.62 (dd, *J* = 3, 15 Hz, 1 H, $H_b$), 2.48 (d, *J* = 15 Hz, 1 H, $H_g$), 2.21–2.28 (m, 1 H, $H_h$), 2.17–2.14 (m, 1 H), 1.95–2.05 (m, 1 H), 1.57–1.66 (m, 2 H), 1.31 (t, *J* = 7 Hz, 3 H, ethyl ester). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 204.8, 169.3, 143.0, 140.8, 128.7, 128.2, 125.6, 115.8, 79.1, 78.0, 69.0, 61.7, 47.1, 33.5, 28.6, 20.2, 14.1. HRMS (+ESI): *m/z* calcd for $C_{19}H_{22}O_4Na^+$ [M + $Na^+$]: 337.1416: found_ 337.1406.
(21) **Characterizations of Selected Products in Table 2**
Oxadecalin **4e**: colorless oil (52%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 5.16 (d, *J* = 2 Hz, 1 H), 4.62 (t, *J* = 3 Hz, 1 H), 4.53 (d, *J* = 2 Hz, 1 H), 4.21–4.28 (m, 2 H), 2.79 (d, *J* = 14 Hz, 1 H), 2.39–2.42 (m, 1 H), 2.24 (d, *J* = 14 Hz, 1 H), 2.13–2.19 (m, 1 H), 1.93–1.98 (m, 1 H), 1.83–1.92 (m, 1 H), 1.48–1.59 (m, 2 H), 1.33 (s, 3 H), 1.28 (t, *J* = 7 Hz, 3 H), 1.26 (s, 3 H). $^{13}$C NMR(125 MHz, $CDCl_3$): δ = 206.0, 169.4, 142.9, 115.7, 75.1, 71.3, 68.2, 61.5, 50.3, 33.6, 30.9, 28.8, 24.3, 19.9, 14.0. HRMS (+ESI): *m/z* calcd for $C_{15}H_{22}O_4Na^+$ [M + $Na^+$]: 289.1416; found: 289.1411.
Oxadecalin **4f** (major): colorless oil (53%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.37 (m, 5 H), 5.27 (d, *J* = 2 Hz, 1 H), 4.59 (d, *J* = 2 Hz, 1 H), 4.55 (t, *J* = 3 Hz, 1 H), 4.33 (d, *J* = 11 Hz, 1 H), 3.81 (3 H, s). 2.99–3.06 (m, 1 H), 2.50 (d, *J* = 15 Hz, 1 H), 2.18–2.24 (m, 1 H), 2.08–2.11 (m, 1 H), 1.95–2.04 (m, 1 H), 1.52–1.63 (m, 2 H) 0.84 (d, *J* = 7 Hz, 3 H). $^{13}$C NMR(125 MHz, $CDCl_3$): δ = 206.4, 169.9, 143.8, 140.0, 128.6, 128.5, 127.0, 115.8, 86.2, 78.2, 69.4, 52.6, 48.8, 33.6, 28.7, 20.2, 9.5. HRMS (+ESI): *m/z* calcd for $C_{19}H_{22}O_4Na^+$ [M + $Na^+$]: 337.1416; found: 337.1433.
Compound **4g**: colorless oil (70%). $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.41 (m, 5 H), 5.34 (t, *J* = 2 Hz, 1 H), 5.06 (t, *J* = 2 Hz, 1 H), 4.79–4.84 (m, 2 H), 4.25 (q, *J* = 7 Hz, 2 H), 2.74–2.88 (m, 1 H), 2.72 (dd, *J* = 12, 16 Hz, 1 H), 2.62–2.68 (m, 1 H), 2.56 (dd, *J* = 3, 16 Hz, 1 H), 2.16 (q, *J* = 7 Hz, 1 H), 1.71–1.85 (m, 1 H), 1.30 (t, *J* = 7 Hz, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 202.7, 168.9, 146.7, 140.2, 128.7, 128.3, 125.7, 113.6, 85.6, 77.7, 72.7, 62.0, 45.0, 31.1, 29.6, 14.1. HRMS (+ESI): *m/z* calcd for $C_{18}H_{20}O_4Na^+$ [M + $Na^+$]: 323.1259; found: 323.1255.
(22) Adams, T. C.; Dupont, A. C.; Carter, J. P.; Kachur, J. F.; Guzewska, M. E.; Rzeszotarski, W. J.; Farmer, S. G.; Noronha-Blob, L.; Kaiser, C. *J. Med. Chem.* **1991**, *34*, 1585.