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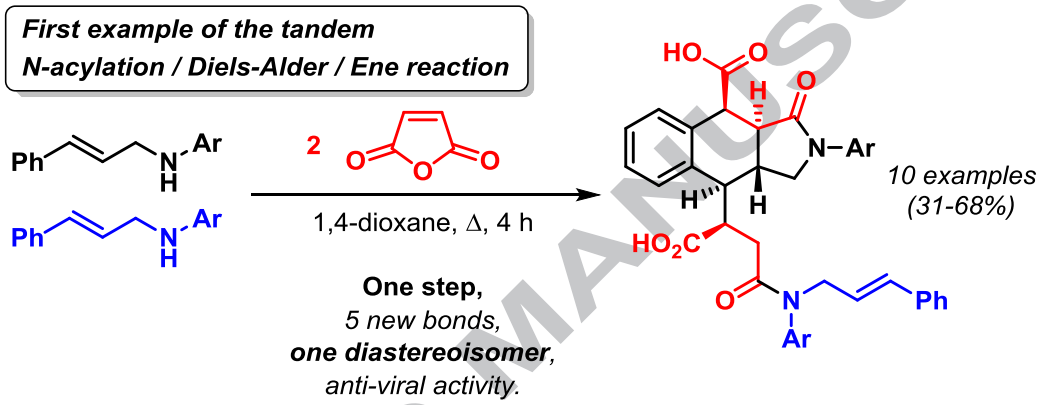

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First example of the cascade acylation/ IMDAV/ ene reaction sequence, leading to *N*-arylbenzo[*f*]isoindole-4-carboxylic acids possessing anti-viral activity.

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ABSTRACT

The reaction between readily accessible *N*-aryl-3-phenylallylamines and maleic anhydride led to unexpected products – polysubstituted hydrogenated benzo[*f*]isoindole-4-carboxylic acids. This transformation proceeds through a previously unknown sequence of steps: *N*-acylation of the allylamine with maleic anhydride, intramolecular Diels-Alder reaction of the vinylarene in the intermediate *N*-maleamide, and Alder-ene reaction of the products of the previous two steps. Selected benzo[*f*]isoindoles displayed antiviral activity.

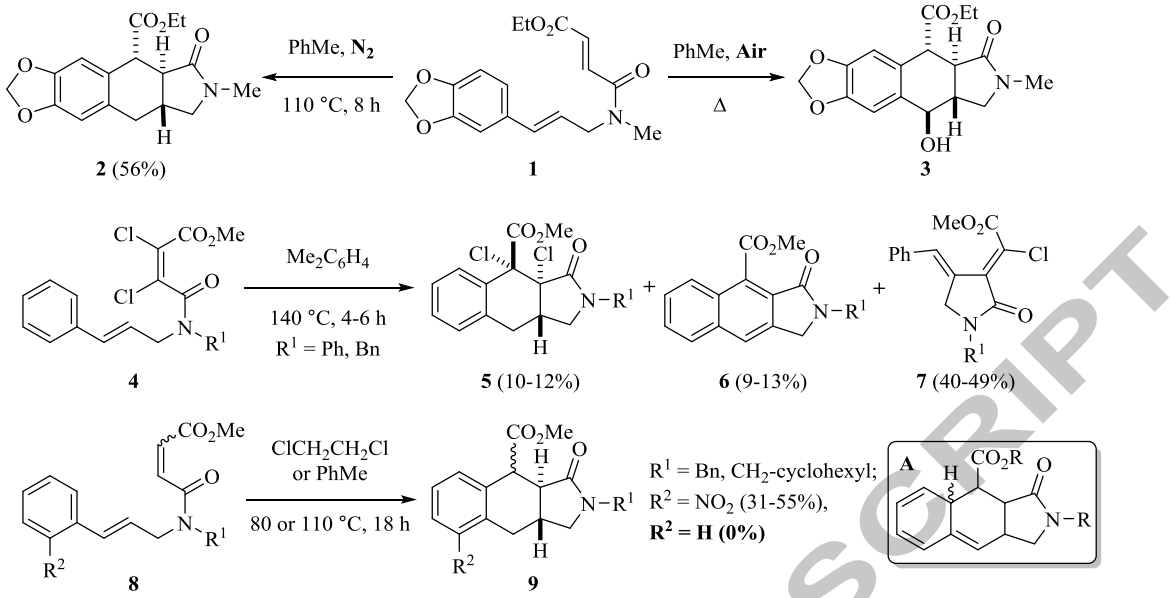
The intramolecular Diels-Alder reaction of vinylarenes (IMDAV reaction) and dienes,[1] particularly styrenes, represents a useful transformation for the synthesis of annulated carbo- and heterocycles. Despite the fact that the transition state of the cycloaddition includes dearomatization of the benzene ring and requires relatively harsh conditions, this methodology is widely adopted in organic synthesis due to the ready availability of the styrene starting materials, and the simplicity of the experimental procedure. More interesting features of the IMDAV reaction are usually exhibited if the reaction is involved in a cascade of consecutive transformations. For example, the tandem IMDAV / Alder-ene reaction[2,3] proceeding through nonaromatic intermediates can serve as a pathway towards polyfunctional condensed arenes. The presence of an external enophile is necessary in all known reactions of this type.[3]

Closely related reactions to the novel transformation reported herein are depicted in Scheme 1. The first successful IMDAV / Alder-ene reaction sequence was demonstrated in 1975 by the intramolecular cyclization of amide **1**.[4a] The possibility for the involvement of a styrene fragment in the thermal intramolecular Diels-Alder reaction was demonstrated using the example of benzoisoindole (**2**) which was isolated in moderate yield. Should the reaction be carried out without an inert atmosphere, the "ene-reaction" between oxygen and the nonaromatic intermediate 1,3,3a,4,4a,9a-hexahydrobenzo[*f*]isoindole (similar to structure **A**) would have occurred to give hydroxy derivative **3**. It was also noted that a small amount of "dimeric material" of an unknown structure (presumably, similar to **13**, see below) was formed.[4a]

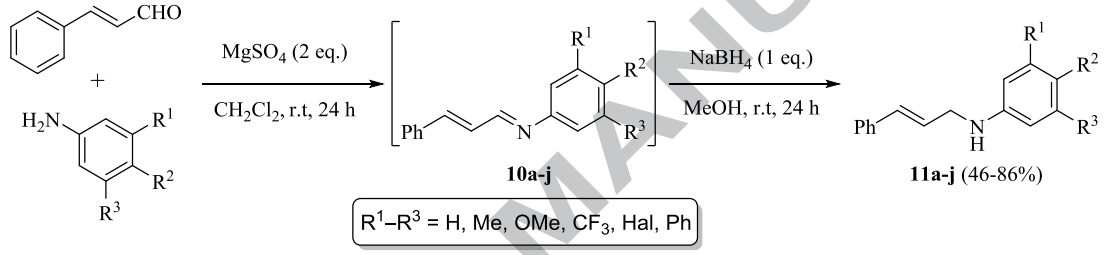
The second example describes the IMDAV reaction of dihalogen amides **4** leading to a mixture in which three products **5-7** were detected, each formed *via* intermediate **A**.[4b] The third and the most recent example, reported that the IMDAV reaction of maleic amides **8** bearing an electron-withdrawing substituent ($R^2 = NO_2$) on the styrene fragment, led to adducts **9** in moderate yields.[4c] At the same time, it was shown that the cycloaddition does not depend on the configuration of the dienophile part of amides **8** (*Z* or *E*-configuration). In contrast, if the initial styrenes **8** are unsubstituted (R^2 = H), a multicomponent mixture is formed under the same reaction conditions. In our opinion, the latter observation is surprising, given the data of the above-mentioned work,[4a] in which the intramolecular cyclization of methylenedioxy substituted styrene (**1**) proceeded smoothly.

We envisioned that our ongoing studies into the IMDAV reaction using 3-furyl- and 3-thienylallylamines,[5] could help explain the ambiguity and therefore, we were encouraged to carry out a detailed study of this reaction in order to investigate the transformation of 3-phenylallylamines under the action of α,β-unsaturated carboxylic acid anhydrides.

The starting materials, 3-phenylallylamines **11a-j**, were prepared from cinnamaldehyde and ring-substituted anilines according to a standard procedure,[5] which involved condensation and reduction steps (Scheme 2).

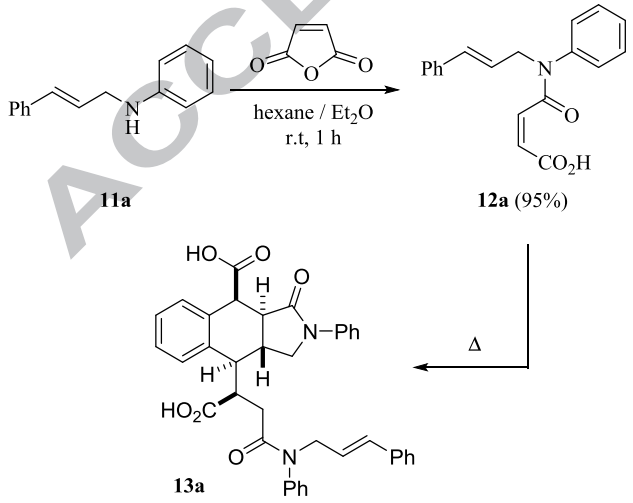


Scheme 1. Previously reported data on the IMDAV reaction of *N*-cinnamylamides (**1**, **4**, **8**).



Scheme 2. Synthesis of *N*-arylcinnamylamines **11a-j**.

The reaction of *N*-phenylcinnamyl amine **11a**, which was used as a model compound, with the simplest and most readily available dienophile maleic anhydride, proceeded quickly (~ 30 min at r.t) to afford maleic amide **12a** in almost quantitative yield (Scheme 3). As established by dynamic NMR experiments (ESI), compound **12a** which possesses diene and dienophile moieties remained almost intact at temperatures below 50 °C. At higher temperatures, the formation of compound **13a** was detected in the reaction mixture.



Scheme 3. Intermediate amide **12a** isolation.

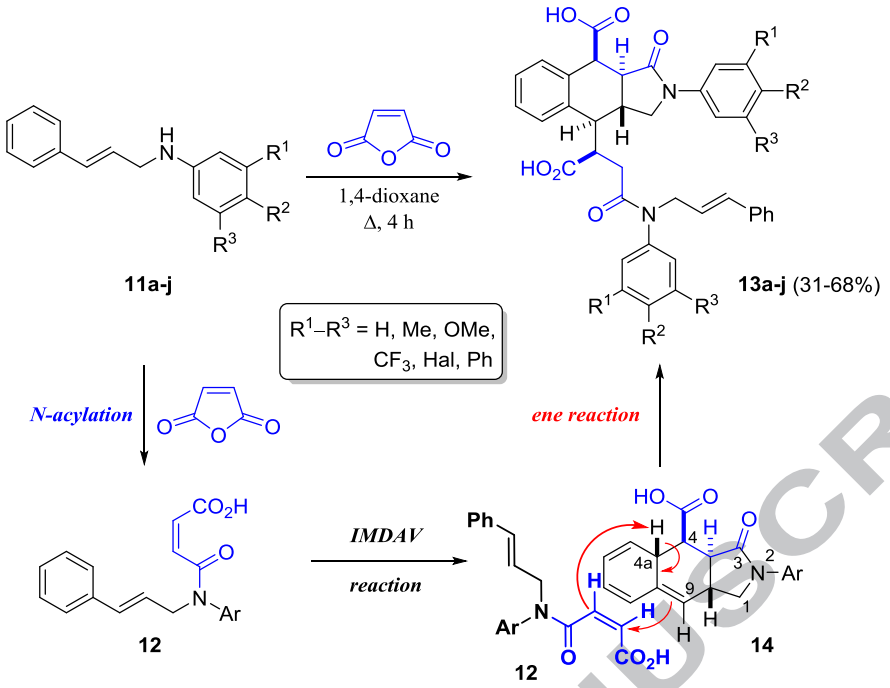
Consequently, it could be proposed with high probability that amides **12** are intermediates in the transformations depicted in Scheme 4.

A subsequent solvent screen revealed that even though THF was suitable for the reaction between **11a** and maleic anhydride, the best yields of compound **13a** (Scheme 4) were obtained with PhH and 1,4-dioxane (Entries 4 and 9, Table 1).

1,4-Dioxane turned out to be more suitable due to a shorter reaction time and easier isolation of products, which are precipitated after concentration of the solution by evaporation and cooling (reactions in PhH required chromatographic purification). Next, the optimum conditions were used for the transformation of allylamines **11b-j** into adducts **13b-j** (Scheme 4, Table 2).

It is worth noting that, at the beginning of this study we anticipated that the main products would be hexahydrobenzo[*f*]isoindoles similar to **2**, **5** and **9** (see Scheme 1). However, thorough analysis suggested that the resulting compound **13**, was composed of two molecules of the initial amine **11** and two molecules of maleic anhydride.

Presumably, after the *N*-acylation of allylamines **11** under the action of maleic anhydride, the IMDAV reaction of amides **12**, leading to the nonaromatic intermediates, benzo[*f*]isoindoles **14**, took place. The subsequent ene-reaction of compounds **12** and **14** proceeds with high regioselectivity, reacting only between the more sterically accessible carbon atom of the double bond of amide **12**, next to the carboxylic group, and the C-9 carbon of the ene-part. Like most pericyclic reactions, the Alder-ene reaction proceeds diastereoselectively, and only one diastereoisomer of **13** was isolated from the reaction mixtures. To the best of our knowledge, this represents the first example of a tandem IMDAV / Alder-ene reaction which does not require the use of an external enophile.



Scheme 4. Plausible mechanism of benzo[*f*]isoindole-4-carboxylic acid **13** formation.

Table 1. Optimization of the IMDAV / ene reaction conditions using the model reaction of cinnamyl amine **11a** and maleic anhydride.[a]

Entry	Solvent	Conditions	Yield **13a** (%)
1	PhH	80 °C, 4 h	44
2	PhH	80 °C, 8 h	53
3	PhH	80 °C, 15 h	71
4	PhH	80 °C, 20 h	77
5	PhH	80 °C, 36 h	70
6	MeCN	80 °C, 20 h	39
7	MeCN	80 °C, 20 h, $ZnCl_2$ (10 mol%)	31
8	THF	65 °C, 30 h	38
9	1,4-dioxane	100 °C, 4 h	68
10	EtOH	78 °C, 2 h	[b]

[a]Reagents and conditions: **11a** (4.0 mmol), maleic anhydride (4.0 mmol), solvent (10 mL). [b]A multicomponent mixture was obtained.

It was difficult to determine the precise spatial structure of the resulting adducts **13** (especially the acyclic part) using NMR analysis due to the occurrence of overlapping proton signals in the low-field region of the ^{1}H NMR spectra. Therefore, to facilitate identification of the structure, single crystal X-ray analysis of compound **13f** (R^1 = MeO, R^2 = R^3 = H) was performed to supplement the NMR analysis (Fig. 1).[6]

Compound **13f** comprises of the fused tricyclic system containing a five-membered (pyrrolidine), six-membered (cyclohexene) and four benzene rings. The five-membered ring has the *envelope* conformation; the deviation of the C-9a carbon atom from the plane of the remaining four atoms (C-1, N, C-3, C-3a) is ~35°. The six-membered cyclohexene ring adopts the *distorted envelope* conformation with the deviation of C-3a ~56°. The hydrogen atoms at C-3a, C-4 and C-9 in **13f** are *cis*-oriented, while the protons H-9 and H-9a occupy the *trans*-positions. The dihedral angle between H-9 and H-9a is 168°. The planes of both *cis*-oriented carboxylic groups are almost parallel. The spatial structure of the other products **13** were assigned by analogy.

Table 2. The substituents (R), yields of compounds **11**, **13**, and the results of anti-viral activity tests for the H1N1 virus using benzo[*f*]isoindole-4-carboxylic acids (**13**).

Entry	R^1	R^2	R^3	Yield **11** (%)	Yield **13** (%)	Anti-viral activity of **13**		
						CC_{50}[a]	IC_{50}[b]	SI[c]
a	H	H	H	69	68	876	570	2
b	H	Me	H	80	41	561	100	6
c	Me	H	H	72	45	294	218	1
d	Me	H	Me	61	31	168	73	2
e	H	MeO	H	46	41	726	396	2
f	MeO	H	H	43	53	659	209	3
g	CF_3	H	H	59	38	31	21	1
h	H	Ph	H	67	52	511	340	2
i	Cl	H	H	86	39	79	71	1
j	H	Br	H	62	68	556	17	33
Rim[d]			N/A			1743	330	6
OC[e]			N/A			>160	0.192	833

[a]50% Cytotoxic concentration (microM), concentration causing death of 50% of cells in the culture. [b]50% Inhibiting concentration (microM), concentration decreasing the viral titer by 50%. [c]Selectivity index (SI), ratio of CC_{50} to IC_{50}. [4d]Rimantadine is the reference compound. [e]Oseltamivir carboxylate is the reference compound.

The original structure of products **13** (containing two amide bonds and a pharmacophore isoindole fragment) motivated us to study its biological properties. The synthesized compounds **13** were tested for cytotoxicity and anti-viral activity using the MTT test and virus yield reduction assay, respectively. In our experiments, we used influenza virus A/Puerto Rico/8/34 (H1N1) that is widely used worldwide as a reference strain,[7] particularly for screening novel potential antiviral agents. It is worth noting that this virus is resistant to first-generation adamantane-based anti-influenza drugs, amantadine and rimantadine.[8]

As shown in Table 2, the compounds under investigation showed varying cytotoxicity. In general, the anti-viral activity of the synthesized compounds was weak, with selectivity indexes ranging from 1 to 6. Unexpectedly, compound **13j** (R^2 = Br, R^1 = R^3 = H) showed low toxicity and the highest anti-viral activity (SI = 33), exceeding that of another effective antiviral ribavirin targeting the influenza virus polymerase complex.[9]

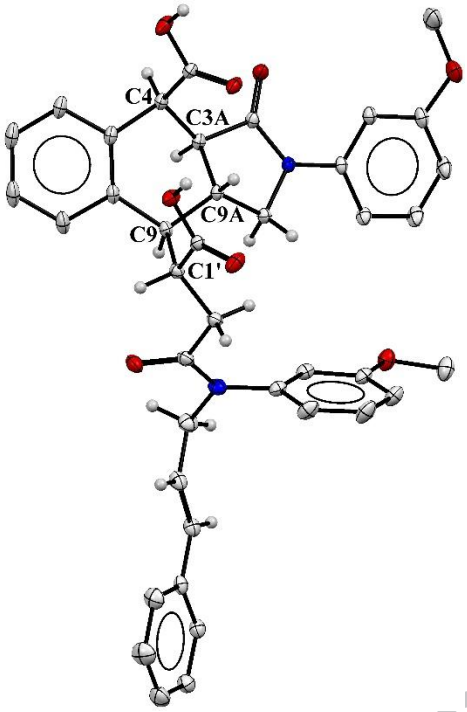


Figure 1. Molecular structures of adduct **13f**. Displacement ellipsoids are shown at the 10% probability level.[6]

In conclusion, the reaction between *N*-aryl-3-phenylallylamines and maleic anhydride unexpectedly revealed that the tandem *N*-acylation/ IMDAV reaction does not stop at the formation of hexahydrobenzo[*f*]isoindoles, but continues *via* the stereoselective Alder-ene reaction leading to polysubstituted hydrogenated benzo[*f*]isoindole-4-carboxylic acids, some of which exhibit antiviral activity against the H1N1 influenza virus.

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References and notes

1. For recent examples of the intramolecular Diels-Alder reaction involving a styrene moiety, see: (a) Yang, B.; Lu, Z. *J. Org. Chem*. **2016**, *81*, 7288. (b) Kocsis, L. S.; Kagalwala, H. N.; Mutto, S.; Godugu, B.; Bernhard, S.; Tantillo, D. J.; Brummond, K. M. *J. Org. Chem*. **2015**, *80*, 11686. (c) Kim, K. H.; Lim, J. W.; Moon, H. R.; Kim, J. N. *Bull. Korean Chem. Soc*. **2014**, *35*, 3254. (d) See a review by Parvatkar, P. T.; Kadam, H. K. Tilve, S. G. *Tetrahedron* **2014**, *70*, 2857, and the references cited therein. (e) Park, J.-E.; Lee, J.; Seo, S.-Y.; Shin, D. *Tetrahedron Lett*. **2014**, *55*, 818. (f) Benedetti, E.; Veliz, A. B. E.; Charpenay, M.; Kocsis, L. S.; Brummond, K. M. *Org. Lett*. **2013**, *15*, 2578. (g) Kocsis, L. S.; Benedetti, E.; Brummond, K. M. *Org. Lett*. **2012**, *14*, 4430. (h) Ozawa, T. Kurahashi, T.; Matsubara, S. *Org. Lett*. **2011**, *13*, 5390.

2. For recent reviews concerning the tandem Diels-Alder / ene-reaction, see: (a) Neier, R.; Banach, E. *Curr. Org. Chem.* **2016**, *20*, 2326. (b) Hack, D.; Blümel, M.; Chauhan, P.; Philippsa, A. R.; Enders, D. *Chem. Soc. Rev*. **2015**, *44*, 6059. (c) Liu, X.; Zheng, K.; Feng, X. *Synthesis* **2014**, *46*, 2241.

3. For recent papers regarding application of the tandem [4+2] / ene reaction, see: (a) Zheng, M.; Wu, F.; Chen, K.; Zhu, S. *Org. Lett*. **2016**, *18*, 3554. (b) Cowell, J.; Abualnaja, M.; Morton, S.; Linder, R.; Buckingham, F.; Waddell, P. G.; Proberta, M. R.; Hall, M. J. *RSC Adv*. **2015**, *5*, 16125. (c) Cowell, J.; Harrington, R. W.; Probert, M. R.; Hall, M. J. *Tetrahedron: Asymmetry* **2015**, *26*, 1189. (d) Bhojgude, S. S.; Bhunia, A.; Gonnade, R. G.; Biju, A. T. *Org. Lett*. **2014**, *16*, 676. (e) Bhojgude, S. S.; Thangaraj, M.; Suresh, E.; Biju, A. T. *Org. Lett*. **2014**, *16*, 3576. (f) Robinson, J. M.; Sakai, T.; Okano, K.; Kitawaki, T.; Danheiser, R. L. *J. Am. Chem. Soc*. **2010**, *132*, 11039. (g) Lodochnikova, O. A.; Ashirov, R. V.; Appolonova, S. A.; Litvinov, I. A.; Plemenkov, V. V. *Russ. J. Org. Chem*. **2010**, *46*, 49.

4. For research closely related to the subject of this work, see: (a) Cox, M. T. *J. Chem. Soc., Chem. Commun.* **1975**, 903. (b) Dawson, J. R.; Mellor, J. M. *Tetrahedron Lett*. **1995**, *36*, 9043. (c) Yamazaki, S.; Sugiura, H.; Ohashi, S.; Ishizuka, K.; Saimu, R.; Mikata, Y.; Ogawa, A. *J. Org. Chem*. **2016**, *81*, 10863.

5. (a) Horak, Y. I.; Lytvyn, R. Z.; Laba, Y.-O. V.; Homza, Y. V.; Zaytsev, V. P.; Nadirova, M. A.; Nikanorova, T. V.; Zubkov, F. I.; Varlamov, A. V.; Obushak, M. D. *Tetrahedron Lett*. **2017**, *58*, 4103. (b) Zubkov, F. I.; Zaytsev, V. P.; Mertsalov, D. F.; Nikitina, E. V.; Horak, Y. I.; Lytvyn, R. Z.; Homza, Y. V.; Obushak, M. D.; Dorovatovskii, P. V.; Khrustalev, V. N.; Varlamov, A. V. *Tetrahedron* **2016**, *72*, 2239. (c) Horak, Y. I.; Lytvyn, R. Z.; Homza, Y. V.; Zaytsev, V. P.; Mertsalov, D. F.; Babkina, M. N.; Nikitina, E. V.; Lis, T.; Kinzhybalo, V.; Matiychuk, V. S.; Zubkov, F. I.; Varlamov, A. V.; Obushak, M. D. *Tetrahedron Lett*. **2015**, *56*, 4499.

6. The colorless crystal of **13f** ($C_{40}H_{38}N_2O_8$, M = 674.72) is triclinic, space group *P-1*, a = 11.993(4) Å, b = 12.821(5) Å, c = 13.603(5) Å, α = 85.446(1)°, β = 63.883(1)°, γ = 66.635(1)°, V = 1712.39(11) Å^3, Z = 2, T = 293 K, μ(MoKα) = 0.009 mm^{-1}, d_{calc} = 1.309 g/cm^3. 26148 total reflections were measured (4.55° ≤ 2Θ ≤ 51°), 6317 unique reflections (R_{int} = 0.0514, R_{sigma} = 0.0382) which were used in all calculations. The final R_1 was 0.0638 (I > 2σ (I)) and wR_2 was 0.1769 (all data).

7. Lin, D.; Li, F.; Wu, Q.; Xie, X.; Wu, W.; Wu, J.; Chen, Q.; Liu, S.; He, J. *Sci. Rep*. **2016**, *6*, 22790.

8. Hussain, M.; Galvin, H. D.; Haw, T. Y.; Nutsford, A. N.; Husain, M. *Infect. Drug Resist*. **2017**, *20*, 121.

9. Krajczyk, A.; Kulinska, K.; Kulinski, T.; Hurst, B. L.; Day, C. W.; Smee, D. F.; Ostrowski, T.; Januszczyk, P.; Zeidler, J. *Antivir. Chem. Chemother*. **2014**, *23*, 161.

Electronic supplementary information (ESI) for this paper is available: single-crystal X-ray description for **13f**, detailed synthetic procedures and spectral data for compounds **11-13**. See DOI:

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Previously unknown tandem N-acylation/ IMDAV / Alder-ene reaction was discovered.

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